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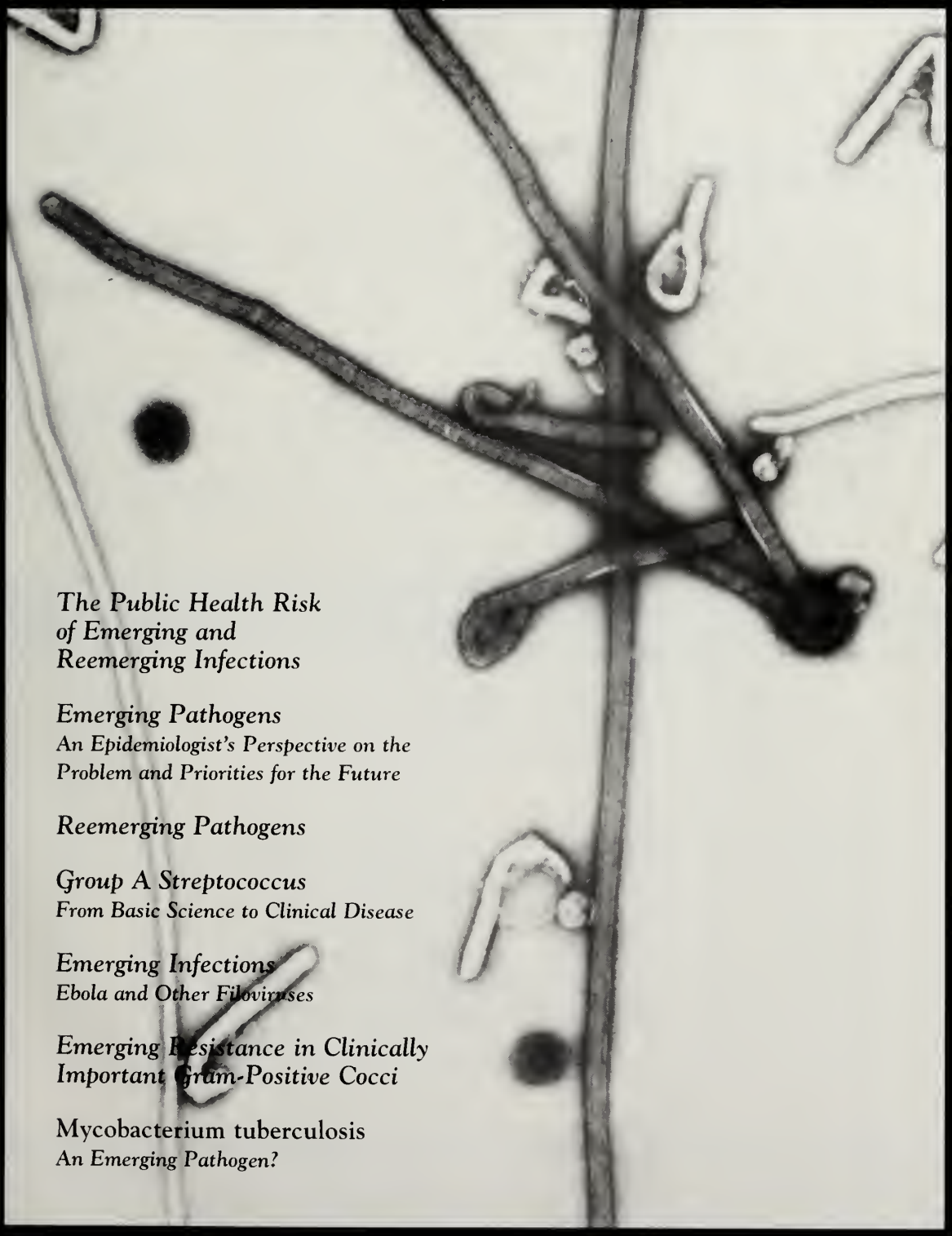
EMERGING GLOBAL MICROBIAL THREATS



The Public Health Risk of Emerging and Reemerging Infections

Emerging Pathogens
An Epidemiologist's Perspective on the Problem and Priorities for the Future

Reemerging Pathogens

Group A Streptococcus
From Basic Science to Clinical Disease

Emerging Infections
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Emerging Resistance in Clinically Important Gram-Positive Cocci

Mycobacterium tuberculosis
An Emerging Pathogen?

Dennis L. Stevens, PhD, MD, Special Editor

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ABSTRACTS JANUARY 1996

(Kuiper JJ: Initial manifestation of primary hyperoxaluria type I in adults—Recognition, diagnosis, and management. West J Med 1996; 164:42-53)

Primary hyperoxaluria type I may initially manifest as urolithiasis, renal insufficiency, or symptoms of systemic oxalosis. This hereditary disorder was fatal until effective therapies evolved during the past two decades. Difficulty in recognizing and diagnosing this disorder in adults is illustrated in a report of a patient eventually restored to good health by high-flux dialysis and combined renal and hepatic transplantation. I explore the molecular processes of the genetic defect and discuss clinical indicators of primary hyperoxaluria type I, manifestations of oxalosis, the pathogenesis of chronic oxalate nephropathy, and the diagnosis and management of this disease.

HYPEROXALURIA, PRIMARY **CALCIUM OXALATE**
KIDNEY FAILURE, CHRONIC

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HYPEROXALURIA, PRIMARY **CALCIUM OXALATE**
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The Western Journal of Medicine

Special Correspondence

The entire September 1995 issue, *Caring for Patients at the End of Life*, generated a large number of *ex cordis* reactions, two of which I share with you to recognize again the work of Christine Cassel, MD, and Gilbert Omenn, MD, as Special Editors. These are the first two letters presented.

In addition, at its November meeting, the California Medical Association's Board of Trustees, reacting to financial pressures, decided to stop printing The Western Journal of Medicine unless we can raise funds to support it and find a permanent publishing alternative (through licensure to a commercial publisher, sale of the Journal, or other arrangements). You can be certain that we have mounted a vigorous campaign to keep the Journal alive and flourishing. Below are excerpts from more than 100 letters that we have received in reply to a letter from me. Other responses have included pledges of interval funding, strong declarations of interest from publishers, and substantial willingness of a sample of readers to increase the amount they pay for subscriptions.

Linda Hawes Clever, MD
Editor

To the Editor: The September issue of The Western Journal of Medicine is a quiet triumph. From the exquisite cover to the range of articles and opinions, it is a beautiful expression of what medicine should represent. And the message conveyed by one of our important journals in taking on this subject shows the profession at its best. Congratulations.

DANIEL D. FEDERMAN, MD
Dean for Medical Education
Harvard Medical School
Baston, Massachusetts

* * *

To the Editor: The copy of the Special Issue of The Western Journal of Medicine (September 1995) is a keepsake. I expect that it will become a textbook equivalent for many students, and it certainly provides rich food for thought for those of us who have followed the literature for many years. The authors have done outstanding jobs. I congratulate you and Christine and Gil on a major contribution.

STUART BONDURANT, MD
Director
The New Yark Academy af Medicine

* * *

To the Editor: In this winter of discontent of medicine, I want to urge you to stay in there. You and your staff do an excellent job of publishing The Western Journal of Medicine. You touch on so many subjects that are not addressed elsewhere, yet are of great importance to the practitioner. I am in your camp.

JOHN F. BURNUM, MD
Tuscalaosa, Alabama

* * *

To the Editor: The Western Journal of Medicine has been one of the most important regional voices in both American and international medicine. Many of the articles that have been published in *WJM* have been useful not only in helping us improve our clinical practice, but also in the stimulation and development of research in medicine. One of the important contributions that the *WJM* makes is that it serves all the branches of clinical medicine. Of particular value to me was a recent issue on addiction medicine [May 1990, Vol 152]. Many of those articles have been useful in both undergraduate and postgraduate medical education.

The availability of the Journal to our medical students has in many instances introduced them to the current medical literature. Medical schools and physicians, not only in the western United States but all over the country, have come to depend on The Western Journal of Medicine as a reliable and valuable source of current medical information.

JOHN N. CHAPPEL, MD
Department of Psychiatry and Behavioral Medicine
University af Nevada Schaal af Medicine
Rena

* * *

To the Editor: The Western Journal of Medicine is a well-respected, widely recognized source of information relevant to physicians in our region and a visible public example of the California Medical Association's commitment to scientific and medical progress and integrity. It seems to me that we should do all we can to retain our collective image as true proponents of those values.

JUDITH MATES, MD
President
San Francisca Medical Saciety

* * *

To the Editor: I have previously been a subscriber to The Western Journal of Medicine and review copies of articles through our local medical library. I can vouch for its use by a number of my fellow colleagues. I trust that you will find sufficient support to keep this excellent journal publishing.

While I'm on the subject of the Journal, please renew my subscription ASAP and send me the bill.

NORMAN J. WILDER, MD, FCCP, FACP
American Callege of Physicians
Ancharage, Alaska

* * *

To the Editor: Over a span of years, The Western Journal of Medicine has provided an invaluable source of information for many physicians throughout the western United States. In these days when the dissemination of practical information that

can assist physicians in their care of patients is essential, its cessation would be a sad loss to a substantial readership. We all know that these are "hard times" in all aspects of medicine, but the one thing we must preserve is the flow of good information to physicians who have ultimate responsibility for the most critical aspect of health care, namely, taking care of patients. In this arena, *WJM* has played, and I hope will continue to play, a very important role.

KENNETH M. MOSER, MD
Department of Pulmonary and Critical Care Medicine
University of California, San Diego, Medical Center

* * *

To the Editor: Although a recent immigrant to the West Coast from Rochester, New York, I have been familiar with the high quality and applicability of the articles in The Western Journal of Medicine throughout my career. It is a highly regarded journal for all clinicians. It deals not only with the direct clinical aspects of medical practice but also many of the broader issues we face as physicians.

HARVEY J. COHEN, MD, PhD
Lucille Salter Packard Children's Hospital
Stanford University School of Medicine
Stanford, California

* * *

To the Editor: The Western Journal of Medicine has stood alone as an example of journalistic excellence. Month after month, it has brought medical information at its best to thousands of readers in the western states.

Each month reading the Journal has been a joy, and the special editions such as "Cross-Cultural Medicine" and "Caring for Patients at the End of Life" will live on as journalistic epics.

Incidentally, as Chair of the Ethical Support Committee for the Kootenai Medical Center, I have been gratified to hear many of my colleagues give this publication words of praise. The Western Journal of Medicine is the publication most sought out by staff physicians.

The Idaho Medical Association was the first state association to join the *WJM* "family." And we have been proud to see the other western states come into the fold. The physicians of Idaho have a deep respect for the Journal and thank the California Medical Association for sharing this great publication with us. May it continue onward with its high purpose.

E. R. W. FOX, MD, FACS
Caeur d'Alene, Idaho

* * *

To the Editor: The Western Journal of Medicine has long been a medical beacon, reflecting the stature and commitment of the California Medical Association to professional standards and growth, as well as an important regional link between the medical societies of the western United States. I recall first reading the Journal as a medical student at the University of Southern California in 1979 and have continued to rely on it for clinical updates, focused reviews, and news of meetings and medical events in our region. Given that many of the states in our regions are "bellwether" states and that their societies have provided active leadership for the rest of our American colleagues, *WJM* has a critical role in medical communication.

PETER M. McGOUGH, MD
Immediate Past President
Washington State Medical Association
Seattle

* * *

To the Editor: The Utah Medical Association has strongly supported this fine publication for the past 18 years and continues to do so.

The Western Journal of Medicine has served as the vehicle for the distribution of our "Utah Medical Bulletin" during those years. More importantly, the Journal has fulfilled its function as an outstanding medical publication. Our committee unanimously expressed its high regard for the Journal and felt that it meets a distinct need for members of the Utah Medical Association.

C. BASIL WILLIAMS, MD
Chair, Editarial Committee
Utah Medical Assaciation
Salt Lake City

* * *

To the Editor: The Western Journal of Medicine holds a unique position among the current publications in that it gives the western region of the country a special forum for publications. More importantly, the Journal often addresses important topics that are not dealt with at all or only from a narrow perspective by other journals.

PATRICIA A. GABOW, MD
CEO
Department af Health and Hospitals
University of Colorado Schaol of Medicine
Denver

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To the Editor: The Western Journal of Medicine continues to provide an important resource for scientific communication for our faculty, fellows, and house staff. I would also note the importance of having a resource for scientific communication that has a regional emphasis. Many important observations and studies would be less attractive to more nationally oriented journals. We continue to be impressed with the high quality of the Journal.

ROBERT G. STRICKLAND, MD
Department of Internal Medicine

R. PHILIP EATON, MD
Vice Chair, Research

RONALD W. QUENZER, MD
Vice Chair, Clinical Affairs

ANN GATELY, MD
Pragram Directar
Internal Medicine Residency Pragram

CURT KAPSNER, MD
Vice Chair, Office af Education

JOSEPH SAIERS, MD
Vice Chair and Chief
VAMC Medical Services

University af New Mexica Schaal of Medicine
Albuquerque

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

February 1-3—**27th Annual Tucson Seminar in Obstetrics and Gynecology and Optional Surgical Anatomy of the Pelvis.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

February 11-15—**International Congress IX on Endovascular Interventions.** Arizona Heart Institute and International Society for Endovascular Surgery at the Phoenician Resort, Scottsdale. Sun-Thurs. Contact: Erika Scott, (602) 266-2200.

February 12-16—**5th Annual Psychopharmacology Review.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Mon. Contact: U of A.

February 15-16—**Samaritan Health System's Biennial HIV Positive/AIDS Conference.** Hyatt Regency, Scottsdale Gainey Ranch, Scottsdale. Sun-Mon. Contact: Linda Luzader, (602) 495-4936.

February 15-17—**Mayo Interactive Surgical Symposium.** Mayo Foundation at Marriott's Camelback Inn Resort, Scottsdale. Thurs-Sat. Contact: Trish Ghan, (602) 301-8323.

February 16-18—**Arizona Society of Anesthesiologists: Anesthesia for the '90s.** University of Arizona College of Medicine at the Doubletree Paradise Valley Resort, Paradise Valley. Fri-Sun. Contact: U of A.

February 17—**Ninth Epilepsy Update: Seizures at All Ages.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Sat. Contact: U of A.

February 19-22—**State-of-the-Art Echocardiography (1626).** American College of Cardiology at Sheraton El Conquistador, Tucson. Mon-Thurs. 25.5 hrs. Contact: (800) 257-4739.

February 22-24—**5th Biennial Geriatric Medicine Update and Certification Exam Review Course.** University of Arizona College of Medicine at the Westin La Paloma Resort, Tucson. Thurs-Sat. Contact: U of A.

March 3-6—**10th Annual Magnetic Resonance Imaging Conference.** St Joseph's Hospital and Medical Center and Barrow Neurological Center at the Phoenician Resort, Scottsdale. Sun-Wed. Contact: (602) 406-3067.

March 7-9—**23rd Annual Symposium: Recent Advances in Neurology and Neurosurgery.** St Joseph's Hospital and Medical Center and Barrow Neurological Institute at the Phoenician Resort, Scottsdale. Thurs-Sat. Contact: (602) 406-3067.

March 7-10—**19th Annual Mid-Winter Symposium: Advances in Obstetrics and Gynecology.** Maricopa Medical Center and Phoenix OB/GYN at the Radisson Resort Hotel, Scottsdale. Thurs-Sun. Contact: Cathy Clifton, (602) 267-5366.

March 10-14—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at the Marriott's Camelback Inn, Scottsdale. Sun-Thurs. Contact: Vivian Woods, (313) 763-1400.

March 13-16—**International Conference on the Adjuvant Therapy of Cancer.** University of Arizona College of Medicine at the Wyndham Paradise Valley Resort, Scottsdale. Wed-Sat. Contact: U of A.

March 21-23—**Ophthalmic Reviews 1996: Oculoplastics from Coast to Coast.** Mayo Clinic-Scottsdale at the Radisson Resort, Scottsdale. Thurs-Sat. Contact Trish Ghan, Mayo Clinic-Scottsdale.

March 28-30—**5th Annual Urogynecology and Disorders of the Female Pelvic Floor.** Mayo Clinic-Scottsdale at The Points Hilton Resort at Tapatio Cliffs, Phoenix. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale. Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

April 9-13—**New Frontiers in Pain.** Maricopa Medical Center at the Radisson Resort Hotel, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

April 11-13—**21st Annual Primary Care Update.** University of Arizona College of Medicine at the Tucson Hilton East, Tucson. Wed-Sat. Contact: U of A.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-7832; (800) 328-5868 or (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

January 30-February 3—**34th Annual Scientific Session of the Western Society of Allergy and Immunology.** Western Society of Allergy and Immunology at Ritz-Carlton Mauni Lani, Big Island of Hawaii. Tues-Sat. Contact: Rebecca Gough, PO Box 1122, Roanoke, TX 76262. (817) 491-2616.

ANESTHESIOLOGY

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 26-29—**5th John J. Bonica Hawaii Pain Conference.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

February 9-10—**Cardiology 1996: Concepts and Controversies.** Mercy General Hospital at Radisson Hotel, Sacramento. Fri-Sat. 7 hrs. Contact: Andrea La Pravotte, Mercy Heart Institute. (916) 733-6966.

February 12-16—**Cardiovascular Conference at Hawaii.** American College of Cardiology at Kohala Coast, Hawaii. Mon-Fri. 20.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739. FAX (301) 897-9745.

March 2-9—**Update: Controversies in Cardiovascular Disease.** UCSD at Stouffer Wailea Resort, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

April 25-27—**Sixth Annual Symposium on Coronary Stenting.** Scripps Clinic & Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

February 12-16—**34th Annual Symposium on Critical Care, Trauma, and Emergency Medicine.** USC at the Las Vegas Hilton Hotel. Mon-Fri. 26.75 hours. $595. Contact: USC.

February 24-March 2—**Pediatric Emergencies**. UCSD at Royal Lahaina, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

March 3-8—**16th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 18-22—**Emergency Medicine Symposium II**. UCSD and BSB at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 27-29—**12th Annual Advances in Emergency Medicine.** USC at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17 hrs. $495. Contact: USC.

May 31-June 6—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. 18 hrs. $250. Contact: USC.

ENDOCRINOLOGY/METABOLISM

March 13-14—**Advances in Endocrinology and Metabolism.** UCSF at Ana Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $320. Contact: UCSF.

March 15-16—**Diabetes Update.** USC at Ana Hotel, San Francisco. Fri-Sat. 10.5 hrs. $255. Contact: USC.

June 7-11—**Molecular Steriodogenesis**. UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

EPIDEMIOLOGY/INFECTIOUS DISEASE

May 1-3—**17th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17.5 hrs. $410. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 1-3—**Neurology for the Non-Neurologists.** UCSD. Thurs-Sat. 21 hrs. $500. Contact: UCSD.

February 16-18—**Office Gynecology and Women's Health for the Primary Care Physician**. Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, P.O. Box 84296, San Diego 92138. (619) 223-2997.

February 17-23—**Perinatal Medicine.** USC at Westin Maui, Hawaii. Mon-Thurs. 20 hrs. $595. Contact: USC.

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

March 20-22—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 15 hrs. $325. Contact: UCSF.

April 1-4—**Primary Care in Paradise: Maui 1996.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 6-13—**Sixth Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kauai Marriott Resort, Kauai, Hawaii. 29 hours. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez, CA 94553. (510) 372-1457.

April 7-12—**Ninth Annual Primary Care Medicine: Update 1996**. UCSF at Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

April 18-21—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hilton Beach and Tennis Resort, San Diego. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 27—**29th Society of Teachers of Family Medicine Annual Spring Conference.** AAFP and Society of Teachers of Family Medicine at the Hyatt Regency at Embarcadero Center, San Francisco. Sat-Wed. Contact: Ray Rosetta, Director of Meetings and Programs, The Society of Teachers of Family Medicine. (800) 274-4512.

May 17-21—**Essentials in Primary Care**. Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

March 2-3—**Gastroenterology 1996**. The Southern California Society for Gastrointestinal Endoscopy and the Southern California Gastroenterology Society Symposium. SCGSS at Century Park Hotel, San Francisco. Sat-Sun. Contact: Joyce M. Fried, 19327 Pauma Valley Dr, Northridge, CA 91326. FAX (310) 312-9279.

INTERNAL MEDICINE

February 9-10—**Advances in Diagnosis and Treatment of Splenic Disorders.** Cedars-Sinai Medical Center at Hotel Sofitel Los Angeles. Fri-Sat. 11.5 hrs. Contact: Bari Laner, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Rm 2211, Los Angeles 90048. (310) 855-2937.

February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in La Jolla. Sat. 7 hrs. $140. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 14-16—**29th Annual Recent Advances in Neurology**. UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 15 hrs. $375. Contact: UCSF.

February 17-22—**Topics and Advances in Internal Medicine**. UCSD at San Diego Marriott. Sun-Thurs. 50 hrs. $595. Contact: UCSD.

March 9-16—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kameula, Hawaii. Mon-Fri. 28 hrs. $595. Contact: USC.

March 15-21— **Internal Medicine 1996.** Continuing Medical Education Associates at the Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego, 92138. (619) 223-2997.

April 11-13—**Recent Advances in Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. Contact: UCSD.

April 20—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 6 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

May 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

NEPHROLOGY

January 31-February 3—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Regency on the Bay, San Diego. Wed-Sat. 24 hrs. $550. Contact: UCSD.

February 1-3—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Hyatt Regency on the Bay, San Diego. Thurs-Sat. 17 hrs. $375. Contact: UCSD.

OBSTETRICS/GYNECOLOGY

February 10-13—**51st Annual Postgraduate OB/GYN Assembly**. Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton Hotel, Beverly Hills. Sat-Tues. 22 hrs. Contact: Director, 5820 Wilshire Blvd #500, Los Angeles 90036. (213) 937-5514.

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

January 29-February 2—**Occupational and Environmental Medicine I.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $725. Contact: UCSF.

ONCOLOGY

February 19-22—**Clinical Hematology and Oncology: 1996.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii, on Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OPHTHALMOLOGY

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists.** Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

OTOLARYNGOLOGY

February 3-7, March 2-6, April 13-17—**Temporal Bone Dissection Course.** House Ear Institute in Los Angeles. 48 hrs. $1,300. Contact: Antonio De la Cruz, MD, 2100 W Third St, Los Angeles 90057. (213) 483-4431 ext 7079.

February 23-25—**65th Midwinter Clinical Conference for Ophthalmologists and Otolaryngologists**. Research Study Club of Los Angeles at Sheraton Universal Hotel, Universal City. Fri-Sun. Contact: Louise Ball, PO Box 1216, Murrieta, CA 92564. (909) 677-4482.

June 22-28—**1995-1996 Skull Base Surgical Dissection Course**. House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles, CA 90057.

June 29-July 4—**Second International Skull Base Congress and the Seventh Annual Meeting of the North American Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Floor, Los Angeles 90057.

July 5-7—**Current Concepts in Allergy and Otolaryngology**. Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital, Continuing Medical Education Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

PATHOLOGY

March 18-20—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Mon-Wed. 20 hrs. $500. Contact: UCSD

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 23-25—**Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

February 3—**3rd Annual Update in Behavioral Developmental Pediatrics**. UCSF at Millberry Union Conference Center, UCSF. Sat. 6.5 hrs. $120. Contact: UCSF.

February 19-21—**Pediatric Update**. Continuing Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

March 1-3—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

March 28-30—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 11 hrs. $350. Contact: UCSD.

April 21-23—**Weaning '96.** USC at Stouffer Renaissance Esmeralda Resort, Palm Springs. Sun-Tues. 10 hrs. $525. Contact: USC.

May 16-18—**29th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 16 hrs. $350. Contact: UCSF.

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians**. UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 15 hrs. $350. Contact: UCSD.

PLASTIC SURGERY

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face**. UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

February 11-13—**29th Annual Recent Advances in Neurology**. UCSF at Ritz-Carlton, San Francisco. Sun-Tues. Contact: UCSF.

February 12-17—**AGPA National Conference and Institute: Toward Total Health: Groups to Heal the Mind and Body.** Northern California Group Psychotherapy Society at San Francisco. Mon-Sat. Contact: Ann Steiner, PhD, NCPGS, 821 E Second St, Ste 203, Benicia 94510. (415) 442-1976.

February 23-24—**Psychopharmacology: When to Use What.** American Psychiatric Association and Nevada Association of Psychiatric Physicians at Golden Nugget Hotel, Las Vegas. Fri-Sat. 16 hrs. Contact: Robert L. Horne, MD, 6000 W Rochelle, Ste 700, Las Vegas 89103. (702) 364-1177. FAX (702) 364-5060.

April 19-21—**West Coast Neuropsychology Conference**. UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. 15.5 hrs. $325. Contact: UCSD.

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS. (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037. (619) 554-8556.

RADIOLOGY

March 10-15—**Neuro- and Musculoskeletal MR.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $425-$625. Contact: UCSD.

March 10-15—**Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $626. Contact: UCSD.

March 10-15—**General Radiology Review Course.** UCLA at Guest Quarters Suite Hotel in Santa Monica. Sun-Fri. 40 hrs. $420. Contact: UCLA.

April 6—**Spring Invasive Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. Contact: UCSD.

April 7-12—**16th Annual San Diego Residents Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $700. Contact: UCSD.

April 7-12—**UCSD Neuro and Musculoskeletal MR Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: UCSD.

April 12-14—**2nd Annual Breast Imaging and Interventions Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sat-Thurs. 22.5 hrs. $550. Contact: UCSD.

SURGERY

February 10—**New Advances in Inflammatory Bowel Disease.** Scripps Clinic and Research Foundation at the Amphitheater of the Green Hospital in La Jolla. Sat. 7 hrs. $140. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 19-22—**Clinical Hematology and Oncology: 1996.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Mon-Thurs. 26 hrs. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 28-March 3—**A Divisional Affiliate of the American Osteopathic Association at Palm Springs Riviera Resort.** Wed-Sun. 37 hrs. $495-$745. Contact: Linda Wahlen, Meeting Planner, Osteopathic Physicians and Surgeons of California, 455 Capital Mall, Suite 230, Sacramento 95804. (916) 447-2004. FAX (916) 447-4828.

March 21-23—**Eighth Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $350-$950. Contact: UCSF.

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD at San Diego. Mon-Sat. 36 hrs. $1,395. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

February 9 and 12—**BLS Instructor.** CPR Seminars at San Leandro. Fri and Mon. 13 hrs. $110. Contact: CPR Seminars, 1933 Davis St, Ste 297, San Leandro 94577 (510) 632-6135.

February 19-23—**Physician Heal Thyself.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

March 2—**The Neuropharmacology of Sleep Medicine.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037. (619) 554-8556.

March 22-23—**Out of the Ashes: Can the Private Sector Save Health Care?** Palo Alto Medical Foundation at Fairmont Hotel, San Francisco. Fri-Sat. 12 hrs. $495. Contact: Nancy Collins, Palo Alto Medical Foundation. (415) 853-2911.

April 27-29—**5th Annual Pain Conference: Primary Care Overview of Pain Management.** UC Davis at Tenaya Lodge at Yosemite, Fish Camp. Sat-Mon. Contact: UC Davis.

May 31-June 2—**38th Annual Scientific Meeting of the American Association for the Study of Headache.** San Diego. Fri-Sun. Contact: AASH, (619) 845-1720.

August 8-11—**38th Annual Postgraduate Refresher Course-Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 1-3—**Your Passport to the Future in Internal Medicine.** American College of Physicians/Colorado Chapter at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deb Foust, ACP, Colorado Chapter, (303) 837-7837.

February 18-23—**22nd Annual Vail Obstetrics and Gynecology Conference.** University of Colorado Health Sciences Center at Vail. Sun-Fri. Contact: U of Colo.

March 1-8—**Colorado Review of Anesthesia.** University of Colorado Health Sciences Center at Marriotts' Vail Mountain Resort. Fri-Fri. Contact: U of Colo.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

March 10-13—**International Conference on the Fetus and Newborn XXX: Novel Therapies for Neonatal Respiratory Disorders.** University of Colorado Health Sciences Center at Aspen. Sun-Wed. Contact: U of Colo.

March 17-22—**Reconstructive Surgery of the Hip and Knee.** University of Colorado Health Sciences Center at the Ritz-Carlton Hotel, Aspen. Sun-Fri. Contact: U of Colo.

March 23-28—**Geriatrics Board Review Course.** University of Colorado Health Sciences Center at Denver. Sat-Thurs. Contact: U of Colo.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

February 16-18—**37th Annual Medical Winter Clinics**. Ada County Medical Society at Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. Contact: Judy Barningham (208) 336-2930 or Marie Chester, (208) 386-2135.

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 23-24—**New Mexico Thoracic Society—24th Annual Meeting**. Santa Fe. Fri-Sat. Contact: Billie Dytzel, (505) 265-0732.

February 24-25—**Mammography: Practical Challenges of the '90s for the Technologist.** X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Sat-Sun. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. FAX (404) 552-9859.

February 24-28—**Mammography: Practical Challenges of the '90s: Managed Care, MQSA, and the Radiologist's New Role as Care Giver**. X-Ray Associates of New Mexico at La Fonda Hotel, Santa Fe. Sat-Wed. Contact: Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773. FAX (404) 552-9859.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe. Santa Fe. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 7-10—**Cardiovascular Conference at Snowbird.** Wed-Sat. 19 hrs. Contact: (800) 257-4739.

February 10-11—**The Frank Walsh Society: Directed to Neuro-Ophthalmologists.** Park Hotel, Salt Lake City. Sat-Sun. Contact: UUSM.

February 15-18—**Brigham-Utah Therapeutic GI Endoscopy Course 1995: Problems, Decisions, Techniques**. Yarrow Hotel, Park City. Thurs-Sun. 25 hrs. $495. Contact: UUSM.

February 15-19—**Second Annual Brigham and Women's/Utah Therapeutic GI Endoscopy Course 1996: Problems and Solutions**. Park City. Thurs-Mon. Contact: UUSM.

February 23-27—**41st Annual Postgraduate Course in Anesthesiology, Cardiovascular Anesthesia.** Snowbird Cliff Lodge. Fri-Tues. 18.5 hrs. Contact: UUSM.

February 25-28—**36th Annual OB/GYN Update.** Yarrow Hotel, Park City. Sun-Wed. 13 hrs. $400. Contact: UUSM.

February 28-March 2—**OB/GYN Update in Maternal-Fetal Medicine.** Yarrow Hotel, Park City. Wed-Sat. 13 hrs. $400. Contact: UUSM.

March 3-8—**Advances in Internal Medicine.** Snowbird Cliff Lodge. Sun-Fri. 20 hrs. $450. Contact: UUSM.

March 3-8—**Update in Clinical Microbiology and Immunology.** Olympia Hotel, Park City. Sun-Fri. 25 hrs. $540. Contact: UUSM.

March 8—**Ophthalmology: Resident/Alumni Day.** Fri. 7 hrs. Contact: UUSM.

March 8-9—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

March 10-15—**18th Annual Winter Psychiatry Conference: New Perspectives in Clinical Practice**. The Menninger Clinic at The Yarrow, Park City. Sun-Fri. 28 hrs. $345. Contact: (800) 288-7377.

March 18-20—**Family Practice Refresher Course**. Salt Lake City Hilton Hotel. Mon-Wed. 27 hrs. Contact: UUSM.

March 22—**Heart Failure Symposium**. University Park Hotel, Salt Lake City. Fri. 5 hrs. $40. Contact: UUSM.

MEDICAL GRAND ROUNDS

February 3-6—**Physical Medicine and Rehabilitation Update.** Olympia Park Hotel, Park City. 16 hrs. Contact: UUSM.

February 3-7—**Clinical Cardiac Electrophysiology Review.** Cliff Lodge at Snowbird, Salt Lake City. 35 hrs. Contact: UUSM.

February 5-9—**Surgical Pathology.** Yarrow Hotel at Park City. 20 hrs. Contact: UUSM.

March 28-30—**4th International Congress on Alport Syndrome.** University Park Hotel, Salt Lake City. Contact: UUSM.

April—**Advanced Techniques in Laryngeal Surgery.** 40 hrs. Contact: UUSM.

April 27—**Advances in the Management of Pain in the Acute and Chronic Settings.** University Park Hotel, Salt Lake City. 6 hrs. Contact: UUSM

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 31-February 4—**CME at Whistler, Canada**. Wed-Mon. Contact: PCMS CME.

February 5-9—**Hazardous Waste Annual Refreshers**. Seattle. Mon-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 22—**Risk Assessment**. Seattle. Thur. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 23—**Risk Communication.** Seattle. Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

February 23—**Review of HIV Infections**. Tacoma. Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

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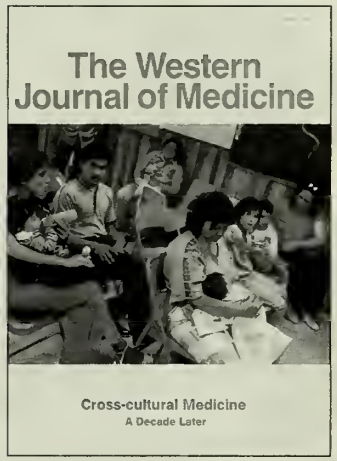

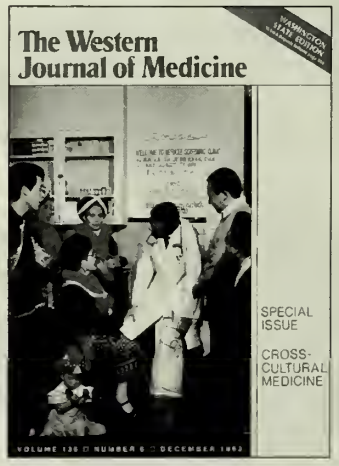

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Global Microbial Threats

Infectious Diseases
Getting Out of a Deep Hole

Deaths from infectious diseases in the United States are on the rise. As Ruth Berkelman, MD, of the Centers for Disease Control and Prevention noted recently, this is true even when infectious disease deaths are age-adjusted. The conclusion? We have a big, urgent problem.

With this special section, THE WESTERN JOURNAL OF MEDICINE joins a worldwide collaboration of medical journals to focus attention on emerging and reemerging infections. The project is the brainchild of George Lundberg, MD, and his colleagues at the *Journal of the American Medical Association*, with help from Magna Nylenna, MD, Editor of the *Journal of the Norwegian Medical Association*, and me. It has many faces. *The American Journal of Medicine*, *British Medical Journal*, *Medicina* (Buenos Aires), *National Medical Journal of India*, and *South African Medical Journal*, along with 37 others, are part of this unprecedented effort. Some of the journals are devoting entire issues to the topic after issuing an open call for papers. The JOURNAL is taking part by publishing this section. Its subjects and authors were carefully selected by Dennis L. Stevens, MD, Chief, Infectious Diseases Section at the Veterans Affairs Medical Center in Boise, Idaho, and Professor of Medicine at the University of Washington School of Medicine in Seattle. We are grateful to all!

We wish to spotlight several areas: risk to communities and individuals, puzzles for clinicians, and opportunities for researchers. We also will enlist the media in an attempt to heighten public interest and concern about these troubling problems. Engaging everyone in an informed, focused campaign against infectious diseases is necessary for a healthy, productive country and world. In many places, for example, tuberculosis is recognized primarily as a consequence of social, economic, and nutritional needs, not simply as a communicable disease. Public advocacy can lead to appropriate measures to eliminate conditions that promote the spread of tuberculosis. Similarly, vaccine research is insufficient, and immunizations often are not given even when vaccines have been developed. This is an indictment of research priorities, litigation, parents, and perhaps public health officials and physicians. Even more so, this points to pernicious social situations that make basic disease prevention an unattainable luxury for some. Involved citizens can make a difference by insisting on action that stops the transmission of devastating illnesses. Furthermore, widespread public awareness can lead to private-public partnerships that can deal effectively with urgent problems. Front-line health care professionals, universities, industry, and the government need to work together to counterbalance disease-driving forces of viral and bacterial mutations, age, war, travel, immunosuppression, poverty, and the inappropriate use of antibacterial and antiviral agents.

Solving the puzzle could be daunting. Because surveillance must increase, medical groups and government entities will need to collect and share information quickly, so that warning mechanisms and interventions can be put into practice. Research must expand. Clinicians must reconsider time-honored treatments that may now be dangerous to individual patients and the larger community.

Infectious diseases are an international problem. Though racism, nationalism, economics, and politics tend to separate the world into districts and countries, microbes respect no such boundaries.

The purpose of bringing infectious diseases to the fore is not to engender fear, discrimination, or chaos, but rather to encourage responsible action. A wag once said, "The first rule of getting out of a hole is to stop digging." As a nation and world, we have dug ourselves into a big infectious disease hole through complacency, neglect, and ignorance. The best way to stop digging is to start informing. Physicians and others who give direct care, health officers, medical group and health plan leaders, the public at large, and elected officials all need to know the kinds of challenges we face and some possible solutions. Then we all need to get to work. The JOURNAL is pleased to be part of a unique international effort to do so.

LINDA HAWES CLEVER, MD
Editor

Global Microbial Threats

The Public Health Risk of Emerging and Reemerging Infections

MERLE A. SANDE, MD, *San Francisco, California*

In the 1960s and the 1970s, national opinion leaders generally considered the threat of infectious diseases to be of only historical interest. Polio had been controlled and smallpox eliminated; vaccines were becoming available to combat major childhood diseases; antibiotics were available for bacterial, fungal, and parasitic diseases; and antiviral drugs were beginning to come "on line." We faced the future with an arrogant optimism that would soon prove unfounded. New diseases have emerged; some old diseases appear to have become more catastrophic or have now emerged as resistant to antimicrobial therapies.

Why were we wrong to be so optimistic? There are several reasons. First, poverty, pestilence, squalor, and poor sanitation did not disappear and, in fact, have reappeared in many parts of the world. Second, we underestimated the ability or the power of the microorganisms to mutate—to form new species and to adapt to new pressures. We failed to realize how rapidly things can change when you mix a large number of bugs under ideal conditions, in which massive amounts of DNA can be exchanged. Human beings mutate slowly, but there are only a few billion of us, whereas microorganisms outnumber us by numbers we cannot imagine. Because mutations are merely mistakes in the transcription of the genetic code, it has become easy to understand that the more transcriptional events that occur, the greater the potential for mutations to emerge. When environmental pressures are added—antimicrobial agents—selection for these mutations is enhanced. That means that no matter what we do to eradicate microorganisms, they will always be one step ahead of us. The challenge is to closely track their evolution.

Particularly effective melting pots for the development of new life forms are the tropical jungles of Africa, South America, and Southeast Asia. There the incredible diversity of life offers a unique environment for microorganisms to breed and their DNA to be exchanged, leading to the evolution of microorganisms that have as potential hosts a variety of insects, rodents, and nonhuman primates. Mutations emerge at random, as does their search for a host. When a "hit" occurs, a new parasitism results. The microbe and the host may live in peace. If an intruder enters into this life, the nonimmune, nonadapted, and unwanted visitor becomes an accidental host. This intruder may be human, and disease and death may result.

The human immunodeficiency virus (HIV) is a good example of this process. Sometime in the recent past, a virus now called SIV (simian immunodeficiency virus) developed a "peaceful" symbiotic relationship with macaques. The virus did not make the monkeys sick; however, it can kill other monkeys if it should find such an accidental host. Sometime later, humans apparently got in the way, and with a minor mutation (less than 10% of the virus RNA changed) HIV-2, a human pathogen, resulted. This virus probably later mutated into HIV-1 and became more virulent to humans, causing the disease we now call the acquired immunodeficiency syndrome. We do not know when this mutation occurred. The earliest serum specimen that I am aware of that contained antibody to HIV-1 came from equatorial Africa in 1957 or 1958, although it is possible that the virus may have been dormant for generations before it began to spread through the human population. Then, with the urbanization of Africa, farmers and their families started migrating into cities. Overcrowded shantytowns sprang up, and poverty was rampant. Many women turned to sex for survival. Sexually transmitted diseases emerged at epidemic rates. The virus found a fruitful mechanism to spread, and the result was that a large number of Africans became infected. Air travel enabled the virus to make it to Haiti and then to New York, Los Angeles, and San Francisco. Now we are in the midst of one of the largest pandemics the world has ever seen. The World Health Organization predicts that four and a half years from now, as many as 50 million persons or perhaps more will be infected, with no vaccine or cure in sight.

Anxiety over the emergence of new viruses has been fueled recently by the media and the movie industry. The Ebola and Marburg viruses appear to be new. The Marburg virus is named for Marburg, Germany, where in 1967 a shipment of sick monkeys from Uganda and Kenya caused 31 cases of human infection and 7 deaths.

(Sande MA: The public health risk of emerging and reemerging infections, *In* Emerging and Reemerging Global Microbial Threats. West J Med 1996; 164:18-20)

From the Medical Service, San Francisco General Hospital Medical Center, San Francisco, California.

This article is adapted from an address to the Senate of California, Sacramento, July 3, 1995.

Reprint requests to Merle A. Sande, MD, Medical Service, San Francisco General Hospital Medical Center, 1001 Potrero Ave, Rm 5H22, San Francisco, CA 94110.

These occurred first in animal handlers and then in family members; however, the epidemic was contained. In 1976, 55 African villages were hit with a new virus, Ebola, named after a river that runs through the area. In Sudan and Zaire, 600 cases and about 500 deaths resulted before this epidemic eventually burned out. Another example occurred in the "hot zone," a military research station in Reston, Virginia, where monkeys from the Philippine Islands became sick and humans became infected, but no disease resulted. The virus in that case was similar but not identical to the 1976 Ebola virus. Of great concern was the observation that aerosol transmission may have resulted in the virus spreading from monkey to monkey. The epidemic was contained. Finally, recently in Zaire, there was a large Ebola virus outbreak that resulted in many deaths. The virus initially spread to health care workers and then to family members, probably from blood and other body secretions. In December of 1995, the Ebola virus again emerged, this time in Nigeria. We know nothing about this virus—where it hides, where it comes from, or where to expect it next—except how to identify it; it took the Centers for Disease Control and Prevention less than a day to identify the virus once a specimen was obtained.

Imagine a virus that may be spread by coughing. Imagine a 747 jet aircraft filled with passengers in a closed space for 12 hours. Imagine the wide dispersal of these passengers from a landing at Los Angeles International Airport and the five-day incubation period. Could a widespread outbreak happen? Absolutely. Air travel has made us a very vulnerable species.

Lassa fever, which is similar to Ebola and is found mostly in western Africa, is equally worrisome. It has about a 10% to 20% mortality in humans and has been imported to the United States in the past, where it caused several deaths.

Several other emerging or resurgent infectious diseases have appeared during the past five years in epidemics in the western hemisphere. Hantavirus, which has received considerable attention, is probably also a brand new virus. Initially, it appeared in the Four Corners region in the Southwest of the United States a few years ago and produced death in humans within 48 hours. We now know that this virus is similar to ones that produced a hemorrhagic disease with renal failure in Korea and China. We also know that it is carried by mice and probably spread by mouse urine-contaminated dust. Infection occurs after inhalation of these dust particles. The Hantavirus has been identified throughout the United States (for example, in California, particularly in the Sierra Nevada region). We have no effective therapy or vaccine for this catastrophic infection.

Yellow fever has now reappeared in the western hemisphere. A 1995 outbreak in South America has had a high mortality. This virus was responsible for many deaths during the Spanish-American War in Cuba. Investigators from the Walter Reed group discovered it was spread by mosquitoes. A massive mosquito eradication project was initiated that was eventually successful and was associated with the near-disappearance of yellow fever. The mosquito eradication program was not ultimately successful, however, and when it was downsized in recent years, the mosquitoes (especially *Aedes aegypti*) came back in even greater numbers. In addition, we are now faced with a new mosquito, the Asian tiger, which was probably imported into the United States (Houston, Texas) from Japan in water that had collected in used tires. It is an aggressive day biter that lays its eggs in urban dwellings and can spread yellow fever, dengue, and possibly various encephalitis viruses. The recent outbreaks of dengue (a less severe disease than yellow fever) along the Texas border and in the Caribbean have reinforced our concerns about the new mosquito threat.

In the past four years, cholera, long considered a disease of the past, having been gone from the western hemisphere for more than a century, has caused more than a million cases and more than 10,000 deaths in Central and South America. This highly virulent bug was probably introduced into the harbor of Lima, Peru, by bilge water from a ship arriving from the Far East. Local fish and shellfish were infected at the same time that the chlorine in the water supply was decreased, apparently because of a report by the Environmental Protection Agency that implicated chlorine as a cause of cancer. The bug spread rapidly throughout South America, Central America, and into Mexico, especially hitting areas with poor sanitation and poverty. More than 100 cases have occurred in the United States in the past several years, whereas only 10 cases had occurred in the 20 years before, most of which had been in travelers to endemic regions. A dramatic example of this bug's potential occurred on an airplane that landed at Los Angeles International Airport in October 1992 from South America, where a large number of patients were infected and became sick from eating contaminated seafood. Because we get most of our produce in the winter from areas where cholera occurs, diligence is critical in examining imports for possible contamination.

Finally, a subtle but important emerging problem warrants discussion. With many bacterial infections, we are rapidly returning to the preantibiotic era. Common pathogens such as the pneumococcus, which causes otitis media in children and pneumonia in adults, have all of a sudden developed resistance to penicillin in some 50% to 60% of cases in some states. We have not even been testing for resistance because since the mid-1940s, when penicillin became available, it has always been effective. When tests were done at San Francisco General Hospital for resistance in these bacteria, we found that 20% of the pneumococci examined were already resistant to penicillin. Other bacteria have also emerged that are causing infections in hospitals around the country. Some are resistant to every known antibiotic. This problem is just beginning. Why? Mostly because we misuse antibiotics at an incredible rate. For example, acute bronchitis, a common infection, is com-

monly treated with antibiotics despite the fact that they do not do any good at all. In fact, the use of antimicrobial therapy produces selective pressure on the bacteria to develop resistance and then spread. The practice of prescribing antibiotics for infections for which they are of no value is widespread. Soon these drug-resistant bacteria will also be widespread.

What can be done about these actual and possible problems? Because we cannot predict where or when the next epidemic will come, mechanisms must be in place to quickly identify cases, identify the cause, and isolate patients if appropriate. We have such programs in place through our Public Health Departments and Schools of Public Health throughout California.

- It is crucial to maintain and enhance our surveillance systems by keeping the public health infrastructure strong. This infrastructure is critically important for early and aggressive identification of the diseases discussed here.
- In California, we must maintain our excellent state laboratory, where early identification of infecting organisms takes place.
- Public city and county hospitals in the state of California will be absolutely critical for the isolation and treatment of cases when the next epidemic occurs. As the safety net for the control and containment of any new emerging pathogen, these hospitals are a resource we cannot afford to lose.
- Health care for undocumented aliens is essential because the introduction and spread of new pathogens may well take place by this route. A major risk to all of us will arise if we do not encourage our health care professionals to diagnose and treat infections early in this population.

It is clear today, more than at any other time in our history, that we are vulnerable to emerging and reemerging infectious diseases. It will be increasingly difficult to stay one step ahead of disease-causing agents. Therefore, continued support is essential for scientists and universities who are working on these problems.

Emerging Pathogens
An Epidemiologist's Perspective on the Problem and Priorities for the Future

JAMES M. HUGHES, MD, *Atlanta, Georgia*

Infectious diseases are the leading cause of death worldwide and an important cause of death in the United States.[1,2] For example, human immunodeficiency virus infection was the leading cause of death among persons between 25 and 44 years of age in the United States in 1993. Nevertheless, because of the availability of antibiotics and vaccines, considerable complacency has developed over the past 30 years in the United States and other developed countries regarding infectious diseases.

In 1992 an Institute of Medicine (IOM) committee co-chaired by Joshua Lederberg, MD, and Robert Shope, MD, issued a landmark report entitled *Emerging Infections: Microbial Threats to Health in the United States*.[3] The report highlighted this complacency, emphasized the threats posed by microbial agents, identified the factors that contribute to disease emergence and reemergence, stressed the need to heighten vigilance and strengthen response capability, and identified research and training priorities.

The IOM report could not have been more timely. Within six months of its publication, clinicians, microbiologists, and public health officials in the United States were confronted with an interstate food-borne disease outbreak of hemorrhagic colitis and hemolytic-uremic syndrome caused by *Escherichia coli* 0157:H7 linked to undercooked hamburger served by a fast-food restaurant chain[4]; the largest waterborne disease outbreak in US history, which resulted in more than 400,000 cases of cryptosporidiosis in Milwaukee, Wisconsin[5]; and an outbreak of the adult respiratory distress syndrome caused by a previously unrecognized hantavirus in the southwestern United States.[6] Simultaneously, the incidence of nosocomial infections caused by vancomycin-resistant enterococci increased in patients admitted to hospitals, resulting in untreatable infections and concerns that genes mediating vancomycin resistance might be transferred to *Staphylococcus aureus*.[7] In addition, the incidence of penicillin resistance in community-acquired pneumococcal infections increased,[8,9] particularly in those in children in day-care settings. Addressing the major challenges posed by these events required rapid investigation, the use of advanced laboratory techniques, and effective communication of results and recommendations for prevention.

Because more than half of the recommendations in the IOM report were directed at the Centers for Disease Control and Prevention (CDC), the CDC developed a strategy for addressing emerging infections in consultation with outside experts in clinical infectious diseases, microbiology, and public health.[10] The strategy comprises four goals that focus on strengthening surveillance and response capability; addressing applied research priorities; improving prevention and control strategies; and strengthening the public health infrastructure, which has deteriorated dramatically at the local, state, and federal levels.[11] Implementation requires effective partnerships with other federal, state, and local public health agencies, academic institutions, industry, the World Health Organization, and other international organizations and agencies.

The CDC has begun implementing the strategy by taking several steps, including establishing emerging infections programs based in four state health departments: California, Connecticut, Minnesota, and Oregon. These programs involve partnerships between state and local health departments, academic institutions, and other local organizations, including health maintenance organizations. Each program is conducting two core projects focusing on invasive bacterial diseases and the cause of unexplained deaths in persons between the ages of 1 and 49 years. Each state has included two or three additional projects of high priority in their geographic area. The CDC has also started publishing the journal *Emerging Infectious Diseases** to provide timely peer-reviewed information on emerging pathogens and relat-

*For information about receiving and contributing to CDC's new journal, contact Editor, Emerging Infectious Diseases, Mailstop C12, NCID, CDC, 1600 Clifton Rd, Atlanta, GA 30333. The journal may also be accessed electronically. For information, send an e-mail to eidhelp@cidod1.em.cdc.gov.

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control and Prevention
IOM = Institute of Medicine

ed issues and has organized a laboratory training fellowship in collaboration with the Association of State and Territorial Public Health Laboratory Directors.

Strengthening the surveillance and response capacity is critical to the successful implementation of this strategy. Clinicians play an important role in recognizing and reporting cases of emerging and reemerging infections, as illustrated by the *E coli* 0157:H7 outbreak in Washington State and the hantavirus pulmonary syndrome outbreak in New Mexico. To address such challenges and those posed by antimicrobial resistance, linkages among the clinical, academic, and public health communities must be strengthened. Although it is difficult to predict specific future challenges posed by infectious agents, experiences involving plague in India,[12] Ebola hemorrhagic fever in Zaire,[13] Venezuelan equine encephalitis in South America,[14] leptospirosis in Nicaragua,[15] and the increased prelavence of dengue and dengue hemorrhagic fever in the Western Hemisphere[16] during the past year remind us that we live in a global village. These outbreaks emphasize the importance of surveillance, prompt epidemiologic investigation, and the availability of adequate diagnostic laboratory capacity. They also illustrate the global implications of a local problem and provide evidence of the disruption of commerce and industry that can result from the occurrence of infectious disease outbreaks.

We will continue to be confronted by nationwide and international outbreaks, new syndromes caused by long-recognized microbial agents, the threat of another influenza pandemic, and increasing problems posed by drug-resistant organisms. Responding to these threats will require strengthened surveillance and the formation of multidisciplinary response teams with expertise in epidemiology, laboratory science, behavioral science, rodent and vector control, health communications, and media relations.

Infectious diseases are important, evolving, complex public health problems. The prevention and control of infectious disease will increasingly require the application of sophisticated epidemiologic, molecular biologic, statistical, and behavioral approaches and technologies. Integrating epidemiologic and laboratory sciences is critical to the prevention and control of emerging infectious diseases.

REFERENCES

1. The World Health Report 1995: Bridging the Gaps. Geneva, Switzerland. World Health Organization. 1995

2. McGinnis JM, Foege WH: Actual causes of death in the United States. JAMA 1993; 270:2207-2212

3. Lederberg J, Shope RE, Oaks SC Jr (Eds): Emerging Infections: Microbial Threats to Health in the United States. Washington, DC, National Academy Press, 1992

4. Bell BP, Goldoft M, Griffin PM, et al: A multistate outbreak of *Escherichia coli* 0157:H7-associated bloody diarrhea and hemolytic uremic syndrome from hamburgers: The Washington experience. JAMA 1994; 272:1349-1353

5. MacKenzie WR, Hoxie NJ, Proctor ME, et al: A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. N Engl J Med 1994; 331:161-167

6. Nichol ST, Spiropoulou CF, Morzunov S, et al: Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993; 262:914-917

7. Frieden TR, Munsiff SS, Low DE, et al: Emergence of vancomycin-resistant enterococci in New York City. Lancet 1993; 342:76-79

8. Breiman RF, Butler JC, Tenover FC, Elliott JA, Facklam RR: Emergence of drug-resistant pneumococcal infections in the United States. JAMA 1994; 271:1831-1835

9. Hofmann J, Cetron MS, Farley MM, et al: The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; 333:481-486

10. Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States. Atlanta, Ga, Centers for Disease Control and Prevention, 1994

11. Berkelman RL, Bryan RT, Osterholm MT, LeDuc JW, Hughes JM: Infectious disease surveillance: A crumbling foundation. Science 1994; 264:368-370

12. Campbell GL, Hughes JM: Plague in India: A new warning from an old nemesis. Ann Intern Med 1995; 122:151-153

13. Centers for Disease Control and Prevention (CDC): Update: Outbreak of Ebola viral hemorrhagic fever—Zaire, 1995. MMWR 1995; 44:468-475

14. CDC: Venezuelan equine encephalitis—Colombia, 1995. MMWR 1995; 44:721-724

15. CDC: Outbreak of acute febrile illness and pulmonary hemorrhage—Nicaragua, 1995. MMWR 1995; 44:841-843

16. Gubler DJ, Clark GG: Dengue/dengue hemorrhagic fever: The emergence of a global health problem. Emerg Infect Dis 1995; 1:55-57

Reemerging Pathogens

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Respect for infectious diseases has been rekindled in the past few years, ignited by a growing recognition of microbial emergence and adaptability. The appearance of newly recognized pathogens with epidemic potential has been important in fostering a new sense of threat; and in particular, the human immunodeficiency virus (HIV) and the awful pandemic of the acquired immunodeficiency syndrome that it spawned have commanded attention, illustrating as they do the smoldering pathogenic potential of viruses that had heretofore been ecologically contained. The emergence of the Lassa, Marburg, Ebola, and Hantaviruses and the geographic expansion of the dengue virus have underscored the point that new infectious agents are out there and that the combined forces of urbanization, social destabilization, and global travel make it almost certain that more such novel challenges will appear.

Attention to these issues has been growing. The National Academy of Sciences produced a report in 1992 that lent credence and substance to those concerns; in 1995 the Institute of Medicine devoted the scientific session of its 25th annual meeting to the same theme. In addition, numerous symposia have been planned to address the general theme of emerging infections, including one that was sponsored by the University of California at San Francisco at the end of December 1995. Such enhanced awareness is heartening as a sign that the problem is now being taken seriously.

But focusing primarily on novel diseases and agents introduces a perceptive hazard, for the exotic element in the emergence issue tends to dominate. The Ebola virus causes lurid disease, and it comes and goes mysteriously—but somewhere else; in that instance, sustained importation is highly unlikely. Hantaviruses have appeared in the United States and in other parts of the world, but they have been geographically localized, quickly analyzed, and seemingly contained. The temptation is to remain detached from the issues thus raised or else to assume a nihilistic position, at least so far as the realities of medical practice are concerned, because sweeping global population changes and shifts in microbial ecology seem as far from individual practitioners' control as does the hole in the ozone layer.

Yet, the most profound threats stemming from microbial adaptability, in my view, are close to home: I refer to the relentless emergence of antibacterial and antiviral resistance capability among familiar, established human pathogens. The problem of bacterial resistance to previously reliably curative drugs has gone far beyond the simple strategy of switching antibiotics. Examples abound, including as an extreme case the fact that the haunting specter of enterococcal resistance even to vancomycin has become real, and the usefulness of generations of new antibacterial agents can be negated within months of their introduction. In fact, among the great bacterial infectious diseases, only syphilis remains fully susceptible to straightforward treatment protocols; for all the rest, reports are proliferating of microbial resistance against long lists of antibiotics.

There is little doubt that the pressure of antibiotic use throughout our environment has contributed to this unsettling trend, nor is there any question that antibacterial drugs are extensively overused both in the United States and worldwide. The public has developed an expectation that all febrile diseases require active therapy. The pressure on physicians to administer treatment is synergistic with the general momentum of defensive medicine. Furthermore, crowded appointment schedules make it tedious and unwieldy to undertake the necessary job of patient education about viruses and bacteria and the selective use of antibiotics.

That equation is shifting inexorably, however. We are now in a world where streptococci have turned aggressive, where pneumococci remain so, and where *Haemophilus influenzae* would be casting a truly ominous shadow on pediatric populations were it not for the remarkable efficacy (in terms of "herd immunity") of the new conjugated-polysaccharide vaccine. Of course, multidrug-resistant tuberculosis heads the list, if not in numbers, at least in the scale of alarm.

Mycobacterium tuberculosis serves as a useful focus to discuss what can be done. It is still the case that fully and continuously treated tuberculosis responds completely to established regimens. The problems have arisen when treatment has been discontinued or abbreviated and from growing pools of unduly susceptible hosts in whom mycobacteria can get an easy foothold—including those strains that have acquired the tricks of resistance to currently available antituberculous drugs. The good news is that old-fashioned strategies, such as directly observed

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therapy to assure full and continuous treatment, have in fact stemmed the tide in places where they have been deployed. The scare about multidrug-resistant tuberculosis is by no means behind us, but there is reassurance in recent experience—and perhaps some old lessons to be relearned.

Until recently, the dominant response to problems of bacterial resistance—both for *M tuberculosis* and for the broader array of pathogens—has been a call for more antibacterial agents. Clearly, that will remain an important and necessary research goal for the foreseeable future, as the tide of resistant organisms swells, but as a sole response, it makes little sense. We should also devise and endorse with enthusiasm the changes in individual and group practices that would reduce the overuse of antibiotics and decrease their ubiquity in the environment (as, for instance, in agricultural feed as growth adjuncts). It surely is worth the time spent to educate patients about the specificity of antibiotic treatment and the unwisdom of keeping leftovers from prescriptions for self-medicating at a later date. The effect of such careless practices may be far from trivial.

Internationally, the over-the-counter availability of antibiotics makes the situation in this country pale by comparison. But there, too, concerted action may be possible and should be supported. At an Institute of Medicine meeting in October 1995, Stuart Levy, MD, Director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine (Boston, Massachusetts), told of the growing strength of an international collaborative group organized in 1981 and dedicated to fostering and sustaining a decrease in antibiotic use. Entitled the Alliance for the Prudent Use of Antibiotics, it now has participation from nearly 100 countries and has been increasingly effective in coordinating and sharing data about antibiotic use and resistance patterns around the world.*

It is heartening to know of that activity; such worldwide coordination of effort is surely going to be necessary because the fundamental dynamic of both emerging and reemerging infections is that of a world without biologic boundaries. The forces that have made it so—increasing population and migration, urbanization with its associated social upheaval, and international travel—will only intensify in the future.

A final note of concern: all that has been said about antibacterial agents pertains at least as much to antiviral drugs. The creation of clinically useful antiviral agents has proved difficult precisely because resistance arises so regularly—and sometimes quickly. At present, the number of licensed antiviral drugs is small, but they contribute importantly to the care of serious, chronic viral diseases: there are a few for HIV and fewer still for some of the human herpesviruses such as herpes simplex, varicella zoster, and cytomegalovirus. Yet, for each of them, the emergence of resistance has been recorded, and the transmissibility of resultant (resistant) viral strains has been documented.

As their usage expands, it will be important to draw the analogy to antibiotic lessons learned and to endorse and maintain clinical protocols that prevent—or at least forestall—the voiding of their usefulness. With such aspects of emerging and reemerging infections, effective response is not arcane or out of reach, and the practitioner community stands to play a critical role.

*For further information about this group, write to the Alliance for the Prudent Use of Antibiotics, PO Box 1372, Boston, MA 02117-1372.

Group A Streptococcus
From Basic Science to Clinical Disease

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It is not surprising that the spectrum of group A streptococcal (GAS) infections is changing,[1-8] as history is replete with descriptions of epidemics of rheumatic fever, scarlet fever, poststreptococcal glomerulonephritis, erysipelas, and severe pharyngitis. Although all types of GAS infection may occur simultaneously in a community, the prevalence of each illness fluctuates greatly in a given time period. For example, major epidemics of severe scarlet fever have been well described over the course of several centuries. Similarly, the prevalence of rheumatic fever has changed considerably in the past century and currently has reached a nadir in the western world, but the disease remains a major health problem in developing countries. Finally, the prevalence of streptococcal pharyngitis varies widely at different times of the year in all temperate climates.

Although the factors that govern these fluctuations are poorly understood, it is clear that attack rates vary in a cyclical manner. The span of each cycle cannot be accurately calculated because of inconsistent epidemiologic reporting. For example, in the United States, there have been no objective national data on the prevalence of any GAS infection for the past several decades. On the other hand, the Colindale Laboratory in Great Britain has tracked the prevalence of various M types isolated clinically over the past 20 years.[6] Investigators at the laboratory have shown that following the re-emergence of a given streptococcal M type, its prevalence increases, it becomes the dominant M type, and then its prevalence gradually tapers off. Between 1980 and 1990, M type 1 emerged as the dominant strain, and other M types that predominated in the early 1980s virtually disappeared. Interestingly, M-3 strains were found at a lower, but relatively constant, rate throughout this period.

Conventional wisdom suggests that because a specific opsonic antibody against a given M type affords protection, the acquisition of immunity by a substantial proportion of the population would herald the disappearance of that particular strain in that community. This would seem to explain, at least in part, the rise and fall of the prevalence of various M types documented in Great Britain.[6] In Sweden, however, a remarkable epidemiologic phenomenon occurred between 1985 and 1994 in which M type 1 accounted for more than 70% of all the M types identified in clinical specimens.[8] Such a high prevalence had never before been observed. This phenomenon would be understandable if M-1 had never before been seen in that country, but M-1 strains were not newcomers to Sweden or any other country. In fact, M-1 strains have been associated with scarlet fever, rheumatic fever, and streptococcal pharyngitis since before World War II. The likely explanation is that not all M-1 strains are identical. In support of this notion, it has been demonstrated that the *N*-terminal portion of the M proteins among different M-1 strains may vary.[9]

This observation raises two questions: First, will antibody against one M-1 strain be protective against a different M-1 strain? Second, does a minor alteration in the M protein sequence affect its ability to act as a virulence factor? Although this latter question has not been adequately answered, the fact that M-1 strains remain the most common M type isolated from patients with the streptococcal toxic shock syndrome suggests that such phenotypic heterogeneity does not diminish its virulence.[1,3,4,6-8,10,11]

Although some argue that a clone of M type 1 has emerged that has precipitated the recent upsurge of severe invasive GAS infections, it is clear that various M types, such as M-3, M-4, M-6, M-11, M-12, and M-28, as well as nontypable strains, may also cause the streptococcal toxic shock syndrome.[1,3,4,7,8,10,12] Thus, M typing is a powerful epidemiologic tool, yet the role of the different M proteins in the pathogenesis of the streptococcal toxic shock syndrome is poorly understood. It has been shown that among postpartum women, the absence of opsonic antibody against M-1 was significantly associated with the development of invasive GAS infection.[8] This concept fits well with one well established by Lancefield more than 40 years ago, that type-specific antibody affords protection. In light of the recent data regarding phenotypic heterogeneity among M-1 strains, however, we must now consider whether a "subtype" specific antibody is what is required for protection.

We and others have found a strong association

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ABBREVIATIONS USED IN TEXT

GAS = group A streptococcal
IL = interleukin
SPEA [B, C] = streptococcal pyrogenic exotoxin A [B, C]
TNFα = tumor necrosis factor α

between pyrogenic strains of exotoxin A (SPEA) and the streptococcal toxic shock syndrome in the United States.[1,4,7,11,13,14] Not all strains associated with this syndrome produced SPEA, however, and many did not contain the *SPEA* gene.[1,7,8,11,14] Because all strains of GAS contain the gene for pyrogenic exotoxin B (*SPEB*),[14] it was no more a marker for the toxic shock syndrome than it was for less severe GAS infections.[1,7,8,11] The gene for pyrogenic exotoxin C (*SPEC*), like *SPEA*, is transmitted by bacteriophage, and strains producing SPEC alone have most commonly been associated with mild cases of scarlet fever in modern times. Recently two other pyrogenic exotoxins have been identified. Mitogenic factor, or at least the gene for mitogenic factor, has been found in virtually every strain of GAS by gene probe.[15,16] Thus, its role in the streptococcal toxic shock syndrome is not clear at the present time, and streptococcal superantigen (SSA) has been found in an M-3 strain from Idaho, and its role in pathogenesis awaits further study.[17]

All of these exotoxins, and certain M proteins (M-5), have the ability to act as superantigens, causing T-cell proliferation in vitro.[18] It is theorized that some of the manifestations of the streptococcal toxic shock syndrome may be related to the clonal proliferation of specific T-cell subsets bearing specific Vβ repertoires. In addition, these superantigens are potent inducers of the proinflammatory cytokines tumor necrosis factor α (TNFα), interleukin (IL)-1 and IL-6, and the lymphokines, TNFβ, IL-2, and interferon gamma. Recently the mapping of Vβ expression of circulating T lymphocytes was studied in patients with the streptococcal toxic shock syndrome, and surprisingly, there was no expansion of any T-cell subset.[19] In fact, there was apparent deletion of T cells bearing specific Vβ markers. These deleted subsets did not correlate with markers specific for SPEA, SPEB, SPEC, or streptococcal superantigen. This raises several questions. First, did this work define an as-yet-unidentified superantigen specific for the T-cell Vβ subsets deleted? Second, was T-cell clonal proliferation present earlier in the course, that is, before the clinical manifestations of the toxic shock syndrome were apparent? And, finally, by what mechanism did deletion of the specific T-cell subsets occur? Thus, in humans, the role of the pyrogenic exotoxins has not been established.

There seems to be good evidence that cytokines play an important role in the streptococcal toxic shock syndrome. Cytokines such as TNF, IL-1, and IL-6 have been detected in the blood of patients with this disorder, although like endotoxin-induced shock, the quantities of TNF and IL-1 vary.[20] In mouse and baboon models of invasive GAS infections, high levels of TNFα have been measured.[21] Similarly, the administration of an anti-TNFα monoclonal antibody improved survival, attenuated organ failure, and markedly improved the mean arterial pressure.[21]

Although the pyrogenic exotoxins have been most extensively studied, it is clear that other streptococcal components, such as peptidoglycan, lipoteichoic acid, and streptolysin O, are potent inducers of cytokine production by monocytes and macrophages.[22] In addition, SPEB, by virtue of its protease activity, may release IL-1β from pre-ILβ.[23] Finally, SPEA and streptolysin O interact synergistically to induce IL-1β synthesis from mononuclear cells.[20]

In summary, the group A streptococcus has again demonstrated its ability to cause a variety of clinical infections and complications in humans. A more severe side of its infective potential is currently being seen. It is clear that the complexities of its epidemiology are not understood, and although recent investigations have provided some clues to its pathogenesis, we have little insight into the host factors that determine the clinical type of disease. This organism has a unique predilection for the human host, and its multifarious adaptations have made it a successful human pathogen. Luckily its adaptability has not, as yet, resulted in resistance to β-lactam antibiotics. Future directions should include better epidemiologic studies combined with basic science investigations into pathogenesis.

REFERENCES

1. Stevens DL, Tanner MH, Winship J, et al: Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 1989; 321:1-7

2. Bisno AL, Stevens DL: Streptococcal infections in skin and soft tissues. N Engl J Med 1996, in press

3. Stevens D: Streptococcal toxic shock syndrome: Spectrum of disease, pathogenesis and new concepts in treatment. Emerg Infect Dis 1995; 1:69-78

4. Demers B, Simor AE, Vellend H, et al: Severe invasive group A streptococcal infections in Ontario, Canada: 1987-1991. Clin Infect Dis 1993; 16:792-800

5. Brook MG, Bannister BA: Do streptococci cause toxic shock? BMJ 1991; 302:181-182

6. Gaworzewska E, Colman G: Changes in the patterns of infection caused by *Streptococcus pyogenes*. Epidemiol Infect 1988; 100:257-269

7. Schwartz B, Facklam RR, Breiman RF: Changing epidemiology of group A streptococcal infection in the USA. Lancet 1990; 336:1167-1171

8. Holm SE, Norrby A, Bergholm AM, Norgren M: Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988-1989. J Infect Dis 1992; 166:31-37

9. Single LA, Martin DR: Clonal differences within M-types of the group A streptococcus revealed by pulsed field gel electrophoresis. FEMS Microbiol Lett 1992; 91:85-89

10. Martin PR, Høiby EA: Streptococcal serogroup A epidemic in Norway 1987-1988. Scand J Infect Dis 1990; 22:421-429

11. Musser JM, Hauser AR, Kim MH, Schlievert PM, Nelson K, Selander RK: *Streptococcus pyogenes* causing toxic-shock–like syndrome and other invasive diseases: Clonal diversity and pyrogenic exotoxin expression. Proc Natl Acad Sci USA 1991; 88:2668-2672

12. Johnson DR, Stevens DL, Kaplan EL: Epidemiologic analysis of group A streptococcal serotypes associated with severe systemic infections, rheumatic fever, or uncomplicated pharyngitis. J Infect Dis 1992; 166:374-382

13. Cleary PP, Kaplan EL, Handley JP, et al: Clonal basis for resurgence of serious *Streptococcus pyogenes* disease in the 1980s. Lancet 1992; 339:518-521

14. Hauser AR, Stevens DL, Kaplan EL, Schlievert PM: Molecular analysis of pyrogenic exotoxins from *Streptococcus pyogenes* isolates associated with toxic shock-like syndrome. J Clin Microbiol 1991; 29:1562-1567

15. Iwasaki M, Igarashi H, Hinuma Y, Yutsudo T: Cloning, characterization and overexpression of a *Streptococcus pyogenes* gene encoding a new type of mitogenic factor. FEBS Lett 1993; 331:187-192

16. Norrby-Teglund A, Newton D, Kotb M, Holm SE, Norgren M: Superantigenic properties of the group A streptococcal exotoxin SpeF (MF). Infect Immun 1994; 62:5227-5233

17. Mollick JA, Miller GG, Musser JM, Cook RG, Grossman D, Rich RR: A novel superantigen isolated from pathogenic strains of *Streptococcus pyogenes* with aminoterminal homology to staphylococcal enterotoxins B and C. J Clin Invest 1993; 92:710-719

18. Mollick JA, Rich RR: Characterization of a superantigen from a pathogenic strain of *Streptococcus pyogenes* (Abstr). Clin Res 1991; 39:213A

19. Watanabe-Ohnishi R, Low DE, McGeer A, et al: Selective depletion of Vβ-bearing T cells in patients with severe invasive group A streptococcal infections and streptococcal toxic shock syndrome. J Infect Dis 1995; 171:74-84

20. Hackett SP, Stevens DL: Streptococcal toxic shock syndrome: Synthesis of tumor necrosis factor and interleukin-1 by monocytes stimulated with pyrogenic exotoxin A and streptolysin O. J Infect Dis 1992; 165:879-885

21. Stevens DL, Bryant AE, Hackett SP, et al: Group A streptococcal bacteremia: The role of tumor necrosis factor in shock and organ failure. J Infect Dis 1996, in press

22. Stevens DL, Bryant AE, Hackett SP: Gram-positive shock. Curr Opin Infect Dis 1992; 5:355-363

23. Kappur V, Majesky MW, Li LL, Black RA, Musser JM: Cleavage of interleukin 1B (IL-1B) precursor to produce active IL-1B by a conserved extracellular cysteine protease from *Streptococcus pyogenes*. Proc Natl Acad Sci USA 1993; 90:7676-7680

Emerging Resistance in Clinically Important Gram-Positive Cocci

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In the first half of the decade of the 1990s, we in the United States have seen the emergence and escalation of substantial antimicrobial resistance in medically important gram-positive cocci. The incidence of methicillin resistance of *Staphylococcus aureus* continues to increase (now 18%), resulting in many more isolates that are multiply resistant; all *S aureus* isolates are still susceptible to vancomycin. Enterococci, particularly *Enterococcus faecium*, have increasingly developed resistance to penicillin, gentamicin, streptomycin, and vancomycin (the last plasmid-mediated). More than a fourth of *Streptococcus pneumoniae* strains are now resistant to penicillin, and these strains tend to be multiply resistant, including to cephalosporins and macrolides.

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Many species of gram-positive cocci were important pathogens four to five decades ago, but then took a back seat to gram-negative pathogens. Gram-positive cocci have now returned with a vengeance, and these have a greater resistance to many of the antimicrobial agents.

In the 1950s and into the 1960s, the scourge of hospitals in the United States and the rest of the world was *Staphylococcus aureus*. Because penicillin had antistaphylococcal activity, its major use was to treat staphylococcal infections. Staphylococci soon acquired the ability to produce a β-lactamase, however, and became resistant to penicillin. Consequently, the penicillinase-resistant penicillins were developed and introduced in the early 1960s. With the introduction of these newer penicillins and their ability to inhibit or kill β-lactamase–producing staphylococci, gram-positive organisms became less of a problem, and gram-negative organisms became the major nosocomial pathogens. In the latter part of the 1960s through the early 1980s, the leading nosocomial pathogens were gram-negative. In fact, *Escherichia coli* is still the most frequent nosocomial pathogen in the National Nosocomial Infections Surveillance studies (about 100 institutions), and *Pseudomonas aeruginosa* is one of the five most frequent species (Table 1).[1] In recent years, however, gram-positive organisms have reemerged as important nosocomial pathogens. Thus, any developing or increasing resistance to antimicrobial agents that are normally used to treat gram-positive organisms is medically important.

In most staphylococci, and particularly *S aureus*, the incidence of β-lactamase production had developed to a point where essentially all staphylococci were considered, from a clinical point of view, to be resistant to penicillin. Drugs such as methicillin, however, introduced during the early 1960s, were active against the strains that produced penicillinase and, thus, were the major agents for the treatment of staphylococcal infections. Almost as soon as methicillin was introduced to medical use, methicillin-resistant staphylococci were identified and actually continued to be identified in the 1960s and 1970s.[2] In fact, in the 1960s, methicillin-resistant *S aureus* was a major nosocomial pathogen in Europe,[3] even though relatively rare in the United States. Beginning in the 1970s, the number of strains of methicillin-resistant *S aureus* began to increase and has continued to do so.

Penicillin-resistant pneumococci have also been known since the 1960s, but even into the 1980s, the number of penicillin-resistant pneumococci was fairly low in the United States. Although enterococci have always been recognized as bacteria that are innately "relatively resistant" to a large number of antimicrobial agents, up until recent times, they were assumed to be susceptible to certain drugs, such as ampicillin, which was used for therapy for less severe enterococcal infections. They were also assumed to be susceptible to vancomycin and combinations of a penicillin and aminoglycoside, which were used for more severe enterococcal infections.

Resistance in Staphylococci

As early as the mid-1940s, it was shown that a clinical isolate of *S aureus* could produce an enzyme that would inactivate the penicillin drug and confer penicillin resistance to that particular organism.[4] At that time, the enzyme was not called a β-lactamase but is in fact the first description of β-lactamase (or penicillinase) in *S*

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ABBREVIATIONS USED IN TEXT

MIC = minimal inhibitory concentration
NCCLS = National Committee for Clinical Laboratory Standards

aureus. During the late 1940s and 1950s, the number of strains of staphylococci that produced β-lactamase increased to such a level that penicillin-resistant *S aureus* became a definite clinical problem. Indeed, in our latest national surveillance study, 93% of *S aureus* strains identified in the United States produced β-lactamase and were resistant to penicillin (unpublished data). Because of these high rates of β-lactamase production, all *S aureus* strains are considered resistant to penicillin.

In the early 1960s, the first of the penicillinase-resistant penicillins, methicillin, was introduced.[2] This drug was active against all *S aureus* strains, including those that produced β-lactamase and were resistant to penicillin. Other penicillinase-resistant penicillins were soon introduced, such as cloxacillin, nafcillin, and oxacillin. Although penicillinase-resistant penicillins remained major drugs for the treatment of *S aureus* infections, methicillin-resistant staphylococci were described almost as soon as the drug was introduced.[2] After the introduction of methicillin, the number of cases of infection with methicillin-resistant *S aureus* increased greatly in hospitals in Europe, and it became the primary nosocomial pathogen.[3] In the 1960s and even early into the 1970s, the occurrence of methicillin-resistant *S aureus* in US hospitals was rare, but beginning in the 1970s and continuing into the 1990s, the prevalence of methicillin-resistant *S aureus* has increased steadily in US institutions.[1] For many years, these organisms were thought to occur only as pathogens in hospitals, but it is now recognized that they may be found in the community as well. In our recent surveillance studies of institutions throughout the United States, we have found that the overall incidence of methicillin-resistant *S aureus* is 18% (unpublished data), the increase in this organism going from less than 5% in the early 1970s. During the earlier years of increase, methicillin-resistant *S aureus* was shown to be principally a problem in large university-affiliated institutions, but now all hospitals, regardless of size or affiliation, have some level of cases of methicillin-resistant *S aureus* infection.[5]

The staphylococci that are resistant to methicillin and the other penicillinase-resistant penicillins are resistant because they have a unique penicillin-binding protein called PBP2a.[6] The gene for resistance to methicillin is called *mecA* and is incorporated into the chromosome of the *S aureus*. The most important thing about methicillin-resistant *S aureus*, however, is probably not that it is resistant to methicillin, but rather that it is multiply resistant. Many of the methicillin-resistant *S aureus* organisms now identified in the United States in clinical specimens will be resistant to all drugs that are usually tested, except vancomycin. These resistance patterns include resistance to penicillins, cephalosporins, chloramphenicol, the macrolides, lincosamides, tetracyclines (except for minocycline), aminoglycosides, and the fluoroquinolones (Table 2). Only vancomycin is active against all strains of methicillin-resistant *S aureus*. Although these organisms are resistant to most of the drugs that we test, that is not true for methicillin-susceptible *S aureus*. In general, methicillin-susceptible *S aureus* is susceptible to all agents except the β-lactams that are susceptible to hydrolysis by the β-lactamase produced by these organisms.

TABLE 1.—*Most Frequent Nosocomial Pathogens When All Anatomic Sites Are Considered**

Rank	Species
1	*Escherichia coli*
2	Enterococci
3	*Pseudomonas aeruginosa*
4	*Staphylococcus aureus*
5	Coagulase-negative staphylococci

*From the National Nosocomial Infections Surveillance studies.[1]

TABLE 2.—*The Usual Antimicrobial Susceptibility and Resistance of Methicillin-Resistant* Staphylococcus aureus *to Antistaphylococcal Agents**

Generally Susceptible to	*Generally Resistant to*
Vancomycin	Penicillins
Teicoplanin†	Cephalosporins
Minocycline‡	Tetracycline
Rifampin§	Macrolides
Sulfamethoxazole-trimethoprim§	Lincosamides
Coumermycin†	Chloramphenicol
Novobiocin sodium‖	Fluoroquinolones
Fusidic acid†	Aminoglycosides

*The overall incidence of methicillin-resistant *S aureus* in the United States is 18%.
†These agents are not available for therapeutic use in the United States.
‡Most isolates are susceptible to minocycline even though resistant to tetracycline.
§Two thirds to three fourths of isolates are generally susceptible to these agents.
‖Novobiocin is rarely used in human medicine.

The coagulase-negative staphylococci, and particularly *Staphylococcus epidermidis*, have long been recognized as being among the more common antibiotic-resistant bacteria that are identified in hospitals. The most resistant species tend to be *S epidermidis*, *Staphylococcus hominis*, and *Staphylococcus haemolyticus*, which also happen to be the most common species found in clinical specimens. The incidence of methicillin resistance in *S epidermidis* has always been much higher than that found for methicillin-resistant *S aureus*. For example, in the 1970s, 15% to 20% of cases of *S epidermidis* were resistant to methicillin. It is not unusual now to find within an institution that 70% to 80% of *S epidermidis* isolates are resistant to methicillin. Although there is some correlation between a resistance to methicillin and that to other agents, it is not nearly as clear or as pronounced as it is in methicillin-resistant *S aureus*. Like methicillin-resistant *S aureus*, most *S epidermidis* isolates produce β-lactamase and are resistant to penicillins; resistance to methicillin is due to the presence of the novel PBP2a within the strains. Because of the high incidence of multiply resistant *S aureus* and *S epidermidis* in hospitals, and because almost

TABLE 3.—*Screening Tests for High-Level Aminoglycoside Resistance in Enterococci**

Medium	*Antimicrobial Agent*	*Concentration, µg/ml*
Brain-heart infusion broth	Gentamicin	500
	Streptomycin	1,000
Brain-heart infusion agar	Gentamicin	500
	Streptomycin	2,000

*From the National Committee for Clinical Laboratory Standards.[8,9]

all of them are susceptible to vancomycin, vancomycin has become a major antibiotic in terms of the amount used and the dollars spent within US hospitals.

Emerging Resistance in Enterococci

For many years, enterococci have been recognized as being relatively more resistant because they were either resistant or had low-level resistance to many commonly used antimicrobial agents. Despite this, some antimicrobial agents, such as ampicillin, were thought to be active against them. Indeed, for many years there were movements to drop the susceptibility testing of enterococci in clinical laboratories. Enterococcal infections that were not considered to be severe, such as urinary tract infections, were treated with ampicillin. For more serious infections, such as endocarditis due to enterococci, it was considered essential to add a second agent to achieve bactericidal activity and to eradicate the organism, so enterococcal endocarditis was treated with a combination of penicillin and streptomycin that created a synergistic action. It was later discovered that this combination did not always cure patients. The reason was that the enterococcus had developed high-level resistance to streptomycin: synergy between it and penicillin could not be achieved. This high-level resistance was caused by a gene that stimulated the production of an enzyme that inactivated the aminoglycoside. Fortunately, when the organism had high-level resistance to streptomycin, it was susceptible to gentamicin. Thus, gentamicin replaced streptomycin as the aminoglycoside in the combination of penicillin-aminoglycoside therapy for endocarditis. Unfortunately, some enterococci have developed a high-level resistance to gentamicin, resulting in the failure to achieve synergy with a penicillin. Surveillance studies have shown that in the United States, 25% of enterococcal isolates may have resistance to gentamicin.[7] Thus, it is now important to determine possible synergy by testing whether or not the strain of enterococcus shows high-level resistance to the aminoglycoside. The National Committee for Clinical Laboratory Standards (NCCLS), a private, nonprofit organization, has recently published some guidelines for doing these tests (Table 3).[8,9]

It has been shown that strains of enterococci may be resistant to penicillin by two mechanisms. The first is the production of a β-lactamase. The amount of β-lactamase normally produced by an enterococcal strain that is resistant to ampicillin is relatively small. In the usual tests for these strains, resistance may not be evident because there is unlikely to be either an increased minimal inhibitory concentration (MIC) or a smaller zone of inhibition around an ampicillin disk indicating resistance. It is likely that unless a specific test for β-lactamase is performed, such as using nitrocefin, the production of β-lactamase will not be recognized. β-Lactamase-producing enterococci are rare, however, and the likelihood of encountering one in most institutions is not great. The second mechanism for resistance to penicillin in enterococci is the presence of altered penicillin-binding proteins. This is more important than β-lactamase production because it occurs much more often. In fact, the incidence of enterococcal resistance to ampicillin due to altered penicillin-binding proteins is probably near 10% in institutions across the United States.

A third important resistance in enterococci, one that causes great concern among clinicians and microbiologists, is the presence of an inducible vancomycin resistance in enterococci.[10] The threat lies in the source of resistance: a gene that is carried on a plasmid, and the possibility that this vancomycin resistance could be transferred by the plasmid to *S aureus*. This transfer has not yet been demonstrated, and there has yet to be an *S aureus* that is confirmed to be resistant to vancomycin.

The major genes that have been described for resistance in the more clinically important enterococci are the *vanA* and *vanB* genes, but *vanC* genes in *Enterococcus gallinarum* have also been extensively described (Table 4). The MICs for the glycopeptides vancomycin and teicoplanin vary with both *vanA* and *vanB*. Vancomycin resistance due to *vanC* is generally low level. The mechanism for resistance to vancomycin in enterococci involves changes in the membrane of these strains associated with the production of novel proteins.[10] Although many species of enterococci are now recognized, the two major species causing infections in humans are *Enterococcus faecalis* and *Enterococcus faecium*. *Enterococcus faecalis* is by far the most frequent pathogen and probably causes about 90% of the enterococcal infections in humans. The other 10% of infections, for the most part, is due to *E faecium*. This creates a good news, bad news scenario—the bad news is that most of the resistance we see in enterococci occurs in *E faecium*, and the good news is that less than 10% of infections caused by enterococci are due to *E faecium*. The incidence of vancomycin-resistant enterococci is difficult to estimate on a national level because it is a local phenomenon—that is, certain institutions will have clusters with substantial numbers, but most do not.

Development of Resistance in *Streptococcus pneumoniae*

Until recently, good clinical practice considered pneumococci to be susceptible to penicillin and, hence, infections caused by pneumococci would respond to penicillin. Even so, penicillin-resistant pneumococcal isolates had been described in the 1960s in patients in the western Pacific.[11] Penicillin-resistant pneumococci

TABLE 4.—*Enterococcal Species in Which the 3 Major Glycopeptide-Resistant Phenotypes Have Been Observed*

Species	Glycopeptide-Resistant Phenotype		
	vanA	vanB	vanC
Enterococcus foecolis	Yes	Yes	No
Enterococcus faecium	Yes	Yes	No
Enteracaccus gallinarum	No	No	Yes

were described in this country in the 1970s, as well as failures of cases of pneumococcal meningitis to respond to penicillin therapy.[12] Nevertheless, the number of these strains in the United States was low, and this low level continued into the 1980s. During the 1980s, a study at the Centers for Disease Control showed that the incidence of pneumococci with elevated MICs to penicillin was about 5% in the United States.[13] During this time, other surveillance studies also showed that the incidence of penicillin resistance in pneumococci in the United States was about 5%.[14] In the early 1990s, however, we did a surveillance study that showed that the incidence of resistance was about 17% to 20%, depending on the methods used to do the susceptibility testing.[15] The development of penicillin resistance in pneumococci is shown in Table 5.

To understand the development of penicillin resistance in pneumococci, one must understand the break points and the definitions that have been used over the years. The NCCLS considers an MIC of 0.06 μg per ml or less as indicating susceptibility; resistance is shown by an MIC of 2 μg per ml or more.[9,16] The in-between MICs of 0.12 to 1 μg per ml were originally described by us as being relatively resistant and are now described by the NCCLS as being intermediate.[16] Although using MIC tests, as described by the NCCLS, is an excellent method for testing pneumococci, this method was not available to most institutions in the United States when resistance in pneumococci was first being studied. Because most laboratories at that time did disk diffusion tests, it was reasonable that penicillin disk diffusion tests were done. These tests worked well if the MICs were high or low—that is, resistant or susceptible—but did not work well if the MICs were within the relatively resistant or intermediate range. It was found, however, that when the oxacillin disk diffusion test was used as a test for penicillin resistance, a much more accurate result was obtained than when using a penicillin disk.[16] This has come to be known as the oxacillin screening test for penicillin resistance in pneumococci. In this test, the 1-μg disk (the same disk used for testing other species) is used for testing pneumococci. A zone of 19 mm or less indicates resistance, and a zone of 20 mm or more indicates susceptibility to penicillin. When these tests were first described, there was total correlation between these disk diffusion break points and the MIC break points described above.

Although the correlation between the oxacillin disk test and the penicillin MIC break points was initially 100%, this has not remained so. Over the years, more and more strains have been isolated that have MICs of 0.06 μg per ml or 0.03 μg per ml (indicating susceptibility) but yet having zone sizes of 19 mm or less, indicating some degree of resistance. In our 1992 studies, the difference was about 3%, but in our 1995 studies, the difference between these two tests was about 10%. In other words, in the 1995 strains, the resistance by the oxacillin screening test was 10% higher than when tested by MICs (in both cases this includes both resistant and intermediate strains). It has been shown that strains that have MICs of 0.06 μg per ml or less but that have zone sizes of 19 mm or less have altered penicillin-binding proteins. They, therefore, have the mechanism for penicillin resistance, although not enough, apparently, to make the strain resistant.

The mechanism of penicillin resistance in pneumococci, as indicated, is the presence of altered penicillin-binding proteins, which have decreased affinity for penicillin (Table 6).[6] These altered penicillin-binding proteins have a decreased affinity not only for penicillin, but also for cephalosporins. In general, this decreased affinity is more evident in the results with oral cephalosporins, but recently increased resistance to third-generation cephalosporins has become more evident.[17] Penicillin-resistant pneumococci also tend to have increased resistance to the macrolides.[18]

Penicillin resistance in pneumococci has developed slowly over the years, but more recently appears to have increased at a faster rate by increasing from about 5% in the latter part of the 1980s to about 20% in 1991-1992. Apparently substantial increases also occurred in 1995.[17] Also of clinical importance is that the incidence of unmistakably penicillin-resistant strains—that is, strains with MICs of 2 μg per ml or more—has almost tripled nationwide (it was about 2.5% in 1992 and now is >6%). If a pneumococcus exhibits intermediate or relative resistance to penicillin and is causing a case of infection other than meningitis, such as upper respiratory tract infection, it is likely that adequate doses of penicillin could be used for cure, although the amount of clinical data that exist to demonstrate this are limited. It is unlikely, however, that anyone would attempt to use a penicillin, a cephalosporin, or a macrolide for the treatment of an infection due to a strain of pneumococcus having an MIC of 2 μg per ml because the chances are it would be resistant in vitro to these agents (see Table 6). Vancomycin would probably be the drug of choice for

TABLE 5.—*The Development of Resistance to Penicillin in* Streptococcus pneumoniae *in the United States*

Time Period	Incidence, %
Before 1979	Occasional strains
1979 to 1988*	4-5
1991 to 1992†‡	15.2 (MIC)§; 20.1 (oxacillin screen test)‡

*From Spika et al[13] and Jorgensen et al.[14]
†From Thornsberry et al.[15]
‡See Thornsberry et al for indication of further increases.[17]
§The minimal inhibitory concentration (MIC) and oxacillin screening tests are those recommended by the National Committee for Clinical Laboratory Standards.[9]

TABLE 6.—*Correlation of Penicillin Susceptibility in* Streptococcus pneumoniae *and Susceptibility to Other Antipneumococcal Agents*

Penicillin		
Category	*MIC (μg/ml)*	*Correlations*
Susceptible.....	≤0.06	Susceptible to most antipneumococcal agents
Intermediate	0.12-1.0	Some isolates will be resistant to cephalosporins (oral and parenteral) and to macrolides
Resistant.....	≥2.0	Nearly all will be resistant to cephalosporins (oral and parenteral, including third-generation); many will be resistant to macrolides

MIC = minimal inhibitory concentration

such cases because no vancomycin-resistant strains of pneumococci have been identified.

In conclusion, in the first half of the 1990s we have seen increases in antimicrobial resistance in strains of gram-positive cocci of medical importance. This includes the multiple resistance to many antimicrobial agents seen in *S aureus* and *S epidermidis* isolates that are resistant to methicillin; the development of resistance to penicillins, aminoglycosides, and vancomycin in enterococci; and the development of penicillin, cephalosporin, and macrolide resistance in pneumococci. Clearly we need to continue surveillance of these organisms on both a national and a worldwide basis to detect any further increases in antimicrobial resistance in these organisms or for the emergence of new resistances.

REFERENCES

1. Horan T, Culver D, Jarvis W, et al: Pathogens causing nosocomial infections—Preliminary data from the National Nosocomial Infections Surveillance System. Antimicrob Newslett 1988; 5:65

2. Jevons MP: 'Celbenin'-resistant staphylococci. Br Med J 1961; 2:124-125

3. Parker MT: Methicillin-Resistant Staphylococci. Proceedings of the International Conference of Nosocomial Infections. Chicago, Ill, American Hospital Assoc, 1970, pp 112-115

4. Kirby WMM: Extraction of a highly potent penicillin inactivator from penicillin-resistant staphylococci. Science 1944; 99:452

5. Haley RW, Hightower AW, Khabbaz RF, et al: The emergence of methicillin-resistant *Staphylococcus aureus* infections in United States hospitals—Possible role of the house staff-patient transfer circuit. Ann Intern Med 1982; 97:297-308

6. Tomasz A: Penicillin-binding proteins and the antibacterial effectiveness of β-lactam antibiotics. Rev Infect Dis 1986; 8(suppl):S260-278

7. Clark NC, Cooksey RC, Hill BC, Swenson JM, Tenover FC: Characterization of glycopeptide-resistant enterococci from US hospitals. Antimicrob Agents Chemother 1993; 37:2311-2317

8. National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Tests—NCCLS document M2-A5, approved standard edition 5. Villanova, Penn, National Committee for Clinical Laboratory Standards, 1994

9. National Committee for Clinical Laboratory Standards: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—NCCLS document M7-A3, approved standard edition 3. Villanova, Penn, National Committee for Clinical Laboratory Standards, 1994

10. Woodford N, Johnson AP, Morrison D, Speller DCE: Current perspectives on glycopeptide resistance. Clin Microbiol Rev 1995; 8:585-615

11. Hansman D, Bullen MM: A resistant pneumococcus (Letter). Lancet 1967; 2:264-265

12. Paredes A, Taber LH, Yow MD, et al: Prolonged pneumococcal meningitis due to an organism with increased resistance to penicillin. Pediatrics 1976; 58:378-381

13. Spika JS, Facklam RR, Plikaytis BD, et al: Antimicrobial resistance of *Streptococcus pneumoniae* in the United States 1979-1987. J Infect Dis 1991; 163:1273-1278

14. Jorgensen JH, Doern GV, Maher LA, Howell AW, Redding JS: Antimicrobial resistance among respiratory isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the United States. Antimicrob Agents Chemother 1990; 34:2075-2080

15. Thornsberry C, Brown SD, Yee YC, Bouchillon SK, Marler K, Rich T: Increasing penicillin resistance in *Streptococcus pneumoniae* in the US. Infect Med 1993; (Suppl):15-24

16. Swenson JM, Hill BC, Thornsberry C: Screening pneumococci for penicillin resistance. J Clin Microbiol 1986; 24:749-752

17. Thornsberry C, Burton PH, Vanderhoof BH: Increasing resistance to third-generation cephalosporins (TGC) in *Streptococcus pneumoniae*—A 1995 Surveillance Study in the United States. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Late-Breaker Abstract #LB-24, 1995

18. Brown SD, Thornsberry C, Marler JK, Bouchillon SK, Rich TJ, Yee C: Activity of Ofloxacin and Other Antibiotics Against Penicillin-Resistant (Pen^R), Penicillin-Relatively Resistant (Pen^{RR}), and Penicillin-Susceptible (Pen^S) *S pneumoniae*. Am Soc Microbiol 1993; Abstract #A39

Mycobacterium tuberculosis
An Emerging Pathogen?

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It is ironic at best for one of the world's oldest known microbes, *Mycobacterium tuberculosis*, to be considered an "emerging" pathogen. Skeletal abnormalities thought to have been caused by tuberculosis have been recognized in the bones of a neolithic man and in mummified bodies from Egyptian tombs from approximately 1000 BC.[1] More recently, DNA sequences specific for *M tuberculosis* were identified from lesions in a pre-Columbian Peruvian mummy.[2] Clinically, tuberculosis was described accurately by Hippocrates. Although many physicians theorized that tuberculosis was communicable from person to person, the infectiousness of the disease was not proved convincingly until 1865. Less than two decades later in 1882, Koch demonstrated that the organism he identified in material from patients with tuberculosis met the three criteria he had described earlier as being necessary to confirm an etiologic relationship between a microbe and a disease.

The influence of *M tuberculosis* has extended beyond the disease caused by the organism. In many ways, efforts to control tuberculosis present a paradigm for society's approach to disease control and public health in general. The historian and epidemiologist Barbara Rosenkrantz made this point in stating,

> Human history and the tubercle bacillus are so enmeshed that to follow the course of the disease over time is a prerequisite to understanding what the overall struggle to control disease means to ourselves and our contemporary society.[3(p.iii)]

Thus, *M tuberculosis* hardly qualifies as an emerging pathogen. Tuberculosis in the historical sense shares little with, for example, *Clostridium difficile* colitis, legionnaires' disease, hantavirus pulmonary syndrome, or Ebola virus disease, all disorders caused by organisms that have been identified in the past 20 to 25 years. Clearly, it is not the microbe or its recognition that has emerged recently. What has emerged have been the collective heads of the medical, scientific, and public health communities from the sands of indifference and neglect.

Even though *M tuberculosis* is an ancient organism, a number of the factors that have been identified as predisposing to the emergence of "new" pathogens also have influenced the spread of tuberculosis. Population movements within and between countries shift persons from high- to low-incidence areas and cause increased urban crowding, thereby facilitating tuberculosis transmission. Widening economic gradients increase the allure of developed countries for the poor of the developing world. In many parts of the world, worsening economic circumstances, reordering of priorities, and lack of political commitment have all led to a deterioration in the public health infrastructure, just as the need for disease control programs and surveillance is increasing. As a consequence of these and other factors, there are probably more cases of tuberculosis in the world today than ever before. It would be easy to blame human immunodeficiency virus infection for the world's worsening tuberculosis situation, and clearly, it is an important factor. The main effect of the virus, however, has been merely to expose the existing weaknesses of the world's tuberculosis control programs.

Tuberculosis has been called the single largest infectious disease killer in the world.[4] It has long been known and widely reported that tuberculosis causes an estimated 2.5 million deaths a year and that there are 7 to 8 million new cases annually worldwide.[5] Because in most of the world the incidence of tuberculosis is highest in young adults, tuberculosis exacts a tremendous economic and social toll. It has been estimated that, given the economic consequences of the disease and the availability of inexpensive and effective treatment, treatment of tuberculosis is more cost-effective than even oral rehydration therapy for diarrhea.[6] In view of the enormous importance of tuberculosis, why have our heads been in the sand? There are, I think, important lessons in the answers to both this question and the next logical question, What caused our heads to emerge? Why did the disease of Hippocrates, Villemin, and Koch suddenly reappear in the minds of the medical community?

A number of reasons can be cited for the neglect of tuberculosis and that also relate to a rekindling of interest. Probably the most important of these is that for decades about 97% of the world's tuberculosis cases have occurred in nonindustrialized countries.[5] In the United States, the incidence of tuberculosis was decreas-

(Hopewell PC: *Mycobacterium tuberculosis*—An emerging pathogen? *In* Emerging and Reemerging Global Microbial Threats. West J Med 1996; 164:33-35)

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ing by 5% to 6% per year, and similar rates of decline were occurring in most industrialized nations. It was thought that the disease was on its way to eradication. Given the prevailing attitude that tuberculosis was a disease of the past, it is not surprising that it was not accorded a high priority in industrialized countries and that this low priority was conveyed to and adopted by health officials in developing countries. This provincialism on the part of industrialized countries translated to little funding for tuberculosis research and for the support of programs in developing countries. In addition, funding for tuberculosis control programs in the United States was substantially reduced, in part related to the use of a "block grant" mechanism for the federal support of local programs.

The complacent attitude toward tuberculosis was only slightly jarred when, in 1985 and 1986, there was no decrease in tuberculosis case numbers. Yet, by 1993 there had been a 20% increase in the number of cases since 1984. Instead of the expected 5% to 6% per year decline, there were more than 50,000 excess cases. In addition, the specter of tuberculosis caused by organisms that were resistant to isoniazid and rifampin had made an important impression. As a consequence of the increasing number of cases and the appearance of multidrug-resistant disease, the attention paid to tuberculosis increased tremendously. This has translated to increased funding for domestic programs and for research. In addition, because of the funding and public attention, many clinicians and scientists have developed an interest in the disease. This increased interest and awareness should have a long-term beneficial effect on patient care and research.

Part of the reason for the increasing number of cases in the United States is an increasing number of cases among persons born outside of the country. This has led to the recognition by health officials in industrialized countries that tuberculosis is not contained by national boundaries. In 1993 about 30% of persons with newly diagnosed tuberculosis in the United States were foreign-born.[7] Similarly, in many countries in western Europe, 30% to 50% of the cases of tuberculosis were in foreign-born persons.[8] These data show that tuberculosis is a global problem and that tuberculosis control should be a global concern.

The second reason for neglecting tuberculosis is something of a paradox. On the one hand, the international feeling seemed to be that all that was needed to control tuberculosis in developing countries was more assiduous application of available control measures and integration of these measures into primary health care systems. On the other hand, as reflected in an influential series of articles on selective primary health care,[9] tuberculosis was accorded only a medium priority because of the difficulties in applying existing control strategies. These positions interacted in such a way as to cause many health officials to figuratively throw up their hands when it came to providing tuberculosis control. Now it has been well demonstrated that control strategies, such as those developed by the International Union Against Tuberculosis and Lung Disease (IUATLD), can be extremely effective when the political will exists and the system is organized properly.[10] Within the model IUATLD programs, more than 70,000 cases are diagnosed and treated each year, with documented cure rates of at least 75%. These programs have been determined by the World Bank Health Sector Priority Review to be among the most cost-effective of any health intervention in a developing country.[11] Although there are important technical aspects of these programs, the major factor in their success is that they operate in countries where there is a political commitment to the program.

The lack of political commitment to effective tuberculosis control is still a major problem. This is reflected by the woeful inadequacy of funding for tuberculosis control activities by the World Health Organization. Both the internal budget that is largely determined by the World Health Assembly's health ministers from the member nations and extra budgetary funds from donor countries are insufficient to mount an effective international program.

The failure of the scientific community to address the problems related to tuberculosis can be attributed to yet another factor. Besides there being little funding available for tuberculosis research, the organism is not an easy one to investigate. Its rate of growth is slow; it has a tough cell wall; its DNA is guanine and cytosine rich, making sequencing difficult; and high-level biosafety containment facilities are required to work with the organism. Despite these difficulties, modern molecular biology is being applied to *M tuberculosis* successfully, and a number of important advances in understanding the natural processes of the organism have been made.

The challenges confronting tuberculosis control today are both domestic and international. Domestically, it has been demonstrated that with sufficient resources, tuberculosis control measures can be reestablished. This capability is evident in national data and, perhaps most dramatically, in data from New York City, where during the past two years the number of cases has decreased about 21%.[12] The challenge in New York and in the rest of the country will be to maintain adequate funding in the face of a decreasing number of cases. It will be important to convey to those who make funding decisions that the cost per case will necessarily increase as the incidence of the disease decreases and the costs of maintaining an effective program remain fixed.

In addition to programmatic funding, maintaining research funding will be at least an equally difficult task. Clearly, research programs targeted to tuberculosis are paying off. The science has increased phenomenally. It is now up to investigators to use good science to justify continued funding.

The problem is much more severe globally. With a declining incidence of tuberculosis in the United States, there is a real risk of provincialism overtaking us again. In fact, it probably never abated. The amount of international aid for tuberculosis control remains minuscule.

Yet, tuberculosis, because of its natural history, is a much better example of a globally transmitted organism than, for example, Ebola virus. To avoid another pseudoemergence of tuberculosis, a global control strategy should be developed and implemented. Much like the smallpox eradication campaign in which the responsibility for different regions was divided, if the developed countries of North America and western Europe divided responsibility for global tuberculosis control using a strategy coordinated by the World Health Organization, major advances in controlling the disease could be accomplished quickly. We must not collectively submerge our heads in the sands of neglect again.

REFERENCES

1. Morse D, Brothwell DR, Ucko PJ: Tuberculosis in ancient Egypt. Am Rev Respir Dis 1964; 90:524-541

2. Salo WL, Aufderheide AC, Buikstra J, Holcomb TA: Identification of *Mycobacterium tuberculosis* DNA in a pre-Columbian Peruvian mummy. Proc Natl Acad Sci USA 1994; 91:2091-2094

3. Rosenkrantz BG: Introductory Essay: Dubos and tuberculosis, master teachers, *In* Dubos R, Dubos J (Eds): The White Plague, 2nd edition. New Brunswick, NJ, Rutgers University Press, 1987

4. Raviglione MC, Snider DE Jr, Kochi A: Global epidemiology of tuberculosis—Morbidity and mortality of a worldwide epidemic. JAMA 1995; 273:220-226

5. Bloom BR, Murray CJL: Tuberculosis: Commentary on a reemergent killer. Science 1992; 257:1055-1064

6. Murray CJL, Styblo K, Rouillon A: Tuberculosis in developing countries—Burden, intervention, and cost. Bull Int Union Tuberc Lung Dis 1990; 65:6-24

7. McKenna MT, McCray E, Onorato I: The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993. N Engl J Med 1995; 332:1071-1076

8. Rieder HL, Zellweger JP, Raviglione MC, Keizer ST, Migliori GB: Tuberculosis control in Europe and international migration. Eur Respir J 1994; 7:1545-1553

9. Walsh JA, Warren KS: Selective primary health care: An interim strategy for disease control in developing countries. N Engl J Med 1979; 301:967-974

10. Enarson DA: Principles of IUATLD collaborative tuberculosis programmes. Bull Int Union Tuberc Lung Dis 1991; 66:195-200

11. World Bank: World Development Report 1993: Investing in Health. Oxford, UK, Oxford University Press, 1993

12. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA: Tuberculosis in New York City—Turning the tide. N Engl J Med 1995; 333:229-233

Emerging Infections
Ebola and Other Filoviruses

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The images of the bizarre forms of Ebola virus have become familiar to many of us (Figure 1), but the effect of these unique forms on the discoverers of the first known filovirus, the Marburg virus, must have been startling. When the Marburg virus was isolated in 1967, these elongated, irregularly shaped virus particles had the additional context of a new disease with a high mortality transmitted to those caring for the original patients. All that was known was that the virus was imported from Uganda with wild-caught African green monkeys and that it represented a previously unknown group of viruses. What have we learned in the intervening years, and how should we regard these agents?

We now know that the Marburg and Ebola viruses are members of a new virus family, Filoviridae. This family was defined through the morphologic and replicative strategies of the viruses, as contrasted to other single, negative-strand RNA viruses. Their natural history has remained unknown and their clinical appearances infrequent. Indeed, filoviruses are known only from a few isolates in Africa over the intervening years, including those of the Ebola virus in Zaire (1976, 1979, 1995),[1,2] Sudan (1976, 1979), and Ivory Coast (1994) and the Marburg virus in Zimbabwe (1975) and Kenya (1980, 1984, 1987). A series of isolates of another Ebola subtype was identified from 1989 to 1992 from monkeys imported from the Philippines into Reston, Virginia, and other sites in the United States and Siena, Italy.[3] The infrequent isolations are more remarkable for the fact that the Ebola "virus" is actually composed of four subtypes that are 30% to 45% different at the nucleotide level, suggesting that they represent four different viruses. Thus, each filovirus episode, including the three large epidemics (Sudan and Zaire in 1976 and Zaire in 1995),[1,2] is thought to represent only a single or limited introduction of the Ebola virus into the human population with subsequent interhuman transmission. This is likely also the case for the Reston, Virginia, monkey episode in 1989.

Arenaviruses provide an interesting comparison. The identification of Junin and Machupo viruses from cases of Argentine and Bolivian hemorrhagic fever also led to the definition of a new virus family Arenaviridae. The basis for including these viruses with lymphocytic choriomeningitis and Tacaribe viruses was primarily morphologic and serologic. After the definition of the family, new members such as the Lassa fever virus were quickly added. Today there are at least 14 arenaviruses discovered from the Americas, and at least 5 are human pathogens. They all cause chronic infections of rodents, with the possible exception of Tacaribe virus, which is known only through isolates from bats on the island of Trinidad. Arenaviruses can be found regularly in many cases by revisiting previous sites of activity, and cases of both Argentine hemorrhagic fever and Lassa fever appear yearly in the pampas and in west Africa, respectively. Thus, arenaviruses have followed the usual historical course associated with the identification of a new group of viruses; their reservoirs are known, and we understand at least the basics of their transmission in nature. For Argentine hemorrhagic fever and Lassa fever, we have observed thousands of cases of infection in humans from the natural reservoir and the consequences, both clinically and in terms of interhuman transmission. This provides us with a starting point in developing the principles to control human disease and contrasts markedly with the filovirus situation.

Another contrast between arenaviruses and filoviruses lies in the area of treatment. Arenaviruses are sensitive to the antiviral drug ribavirin in cell culture; Lassa fever, and probably other arenavirus diseases, can be successfully treated with the drug. Convalescent plasma is highly effective in therapy for Argentine hemorrhagic fever. Filoviruses have not been susceptible to inhibition in vivo or in vitro by ribavirin. Furthermore, their in vitro neutralization by convalescent plasma is negligible or inefficient, and attempts to treat animals with convalescent plasma have uniformly failed. There is a single rather unconvincing case report of the administration of interferon and convalescent plasma to a person infected with the Ebola virus in the laboratory, and studies of nonhuman primates suggest that hyperimmune horse serum might be effective in the postexposure prophylaxis of Ebola virus infection of baboons.

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ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
Ig = immunoglobulin

In May 1995, the world was faced with another Ebola virus outbreak, this time in the large urban center of Kikwit, Zaire (Figure 1).[1] Several valuable diagnostic modalities developed as a result of the 1989 Reston, Virginia, importation of Ebola-infected monkeys served effectively. The results of antigen-capture enzyme-linked immunosorbent assay (ELISA) were positive in 11 of 13 acutely infected patients from whom specimens were initially taken, and this provided a timely and accurate measure of infection. Immunoglobulin (Ig) M-capture ELISA detects antibodies in recently convalescent patients, and IgG-ELISA seems to have overcome the problems of nonspecificity that have plagued the indirect fluorescent antibody test. The final evaluation of these tests awaits the lengthy process of analyzing specimens by conventional virologic methods. This will also provide the first description of the clinical process of Ebola viral infection in humans; unfortunately, the number of adequate serial specimens collected is limited. These tests are robust enough and free of problems of cross-contamination that they could be taken to the field if trained staff were available and the need were sufficient.

Reverse transcription and polymerase-chain reaction amplification of viral RNA from serum proved to be highly sensitive and had the added advantage of allowing the direct sequencing of the genomic fragment and a definitive diagnosis of the presence of the Zaire subtype of the Ebola virus.[1]

The finding by immunohistochemical staining of extensive skin involvement in human specimens from this epidemic provides both a new diagnostic modality and interesting insights into a possible epidemiologic role for contact contamination (Sherif Zaki, unpublished observations). Moving acute viral specimens from remote African sites to reference laboratories is difficult. Dry ice or liquid nitrogen are usually not available, and the strict International Airline Transport Association rules implemented in January 1995 are complicated and require packing materials that are expensive and not generally available. Thus, the simple step of being able to fix a skin biopsy specimen in formalin and transport it without these considerations opens the way to a more feasible surveillance mechanism, particularly in a disease with a mortality that exceeds 75%, making antibody studies on survivors difficult.

The control of the epidemic required the collaboration of many organizations and strained the budgets and resources available. Thanks to the dedication and efficiency of many courageous Zairians and international workers, it was possible to contain the disease, but not without at least 318 cases, a mortality of 77%, and abortive exportation of the virus to nearby villages. One person infected in Kikwit reached the capital Kinshasa, but there was no further transmission. Dealing with this infectious disease in a town of 250,000 with poor communications and little medical infrastructure was a challenge that fortunately was met successfully. Formal epidemiologic studies of interhuman transmission, still under analysis, confirmed and extended the impressions from previous epidemics.[1,2]

The first reliably identified case occurred in a charcoal worker from Kikwit who died in January 1995, four months before the epidemic was diagnosed. Viral transmission between humans involved close contact with a patient, and proper barrier nursing protected the medical staff. As an example of how difficult it can be to ensure the termination of transmission in such an urban setting,

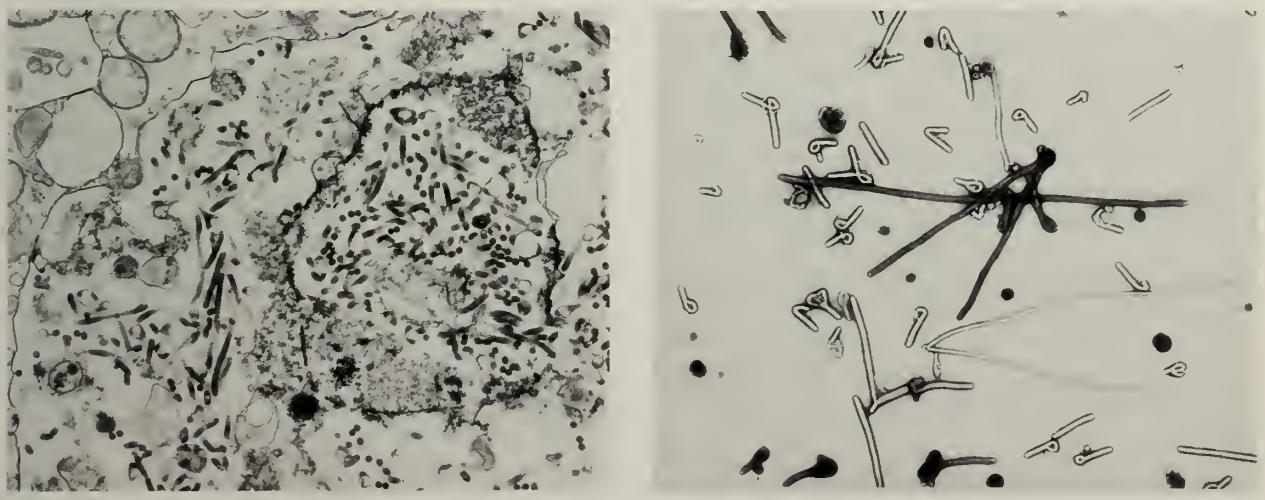

Figure 1.—Electron micrographs of the 1995 Zaire isolate of Ebola virus: **Left,** A thin section of infected Vero cell shows massive production of virions in longitudinal and cross-section. **Right,** A negative stain of whole virions shows shorter replicative forms and longer, irregularly shaped structures. (Courtesy of Charles Humphrey and Cynthia Goldsmith, Cellular and Molecular Pathology Activity, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention.)

immunohistochemical staining of skin specimens revealed one case a month after all participants had agreed that transmission had ceased based on the usual surveillance mechanisms.

Unfortunately, ecologic studies, which were carried out in a collaborative effort among scientists from the United States, Zaire, Belgium, South Africa, and other countries, have not yet yielded any information as to the true virus reservoir that infected the index case of the epidemic. Analysis of the material collected in Zaire will require a major effort and many months of work with no guarantee that any useful positive information will emerge. All laboratory work must be done under biosafety level 4 or maximum-containment conditions in special laboratories to prevent the virus from escaping.

Filoviruses continue to provide a difficult area for virologists to develop strategies to protect the public and can be seen as the prototype of emerging viruses. We do not understand their natural maintenance strategy and thus cannot predict their emergence nor the factors that might reasonably be expected to increase the risk of their presenting problems to the world. Given our profound ignorance of these viruses, the limited number of episodes we have studied, and their lethal potential, it seems a safe bet that we have additional unpleasant surprises in store. The task now is to garner continuing support to understand these elusive agents now that the epidemic has been controlled and public interest has faded.

I would like to acknowledge the many participants in the control and study of the epidemic in Kikwit, some of whom are still working to finish testing of specimens in the laboratory, analyzing data, and preparing detailed and definitive accounts for publication.

REFERENCES

1. Centers for Disease Control and Prevention: Outbreak of Ebola viral hemorrhagic fever—Zaire, 1995. MMWR 1995; 44:381-382

2. Muyembe T, Kipasa M, for the International Scientific and Technical Committee and WHO Collaborating Centre for Hemorrhagic Fevers: Ebola haemorrhagic fever in Kikwit, Zaire (Letter). Lancet 1995; 345:1448

3. Peters CJ, Sanchez A, Feldmann H, Rollin PE, Nichol S, Ksiazek TG: Filoviruses as emerging pathogens. Semin Virol 1994; 5:147-154

Bartonella Species Infections, Including Cat-Scratch Disease, Trench Fever, and Bacillary Angiomatosis

What Molecular Techniques Have Revealed

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The discovery of a new infectious disease syndrome in patients with the acquired immunodeficiency syndrome (AIDS) (bacillary angiomatosis), the return of an old syndrome (trench fever), and the detection of the "mystery" agent of cat-scratch disease have served as a "wake-up call" to those who had concluded that infectious diseases had been conquered by antimicrobial agents and that no new discoveries would be made. The detection and identification of new and old species of *Bartonella*, along with other "emerging" pathogens, were made possible by one of the most important technologic advances in biologic science in this century—the development of methods to detect and identify unique DNA molecules. This technology has revealed a myriad of microorganisms, including new *Bartonella* species, that conventional culture-based methods failed to recognize.

It is estimated that more than 25,000 cases of cat-scratch disease occur in the United States each year, and most epidemiologists think that the true incidence is far higher. Regional lymphadenopathy is the hallmark of infection, and histopathologic examination of node biopsy specimens reveals a typical granulomatous-type inflammation. Systemic signs and symptoms are seen in as many as 50% of patients, and in children serious central nervous system derangements may occur, including encephalopathy and seizures. The causative agent of cat-scratch disease remained a mystery until 1983 when Wear and colleagues reported that by using the Warthin-Starry silver stain, they had visualized tiny bacilli in lymph node specimens from patients with cat-scratch disease.[1] A novel bacillus was later isolated by culture of lymph nodes and named *Afipia felis*.[2,3]

Meanwhile, in 1983 unusual angioproliferative skin lesions were described in a patient with AIDS.[4] This report and subsequent studies demonstrated that these lesions, which morphologically resembled Kaposi's sarcoma, contained tiny bacilli that stained with the Warthin-Starry stain and were identical in appearance to those seen in lymph nodes from patients with cat-scratch disease. Thus, the new syndrome was called bacillary angiomatosis. The nature of the bacilli remained a mystery until 1990 because they could not be cultured in the laboratory. By taking advantage of the relatively new technique of polymerase chain reaction amplification (PCR), Relman and associates at Stanford were able to determine the nucleotide base sequence of the 16S ribosomal RNA gene of the mystery bacillus using oligonucleotide primers that can prime the polymerization of any bacterial 16S ribosomal gene.[5] With the use of these methods, it was discovered that the uncultivatable bacillus embedded in clinical specimens obtained from patients with cutaneous or disseminated bacillary angiomatosis and peliosis hepatis was a novel gram-negative bacillus called BA-TF that was closely related to *Rochalimaea (Bartonella) quintana*. This obscure organism caused trench fever, a prolonged febrile illness associated with bacteremia and systemic manifestations that contributed to serious morbidity of soldiers fighting in Europe in World War I.[5] Virtually no reports of the disease or the isolation of the microorganism had appeared in the English-language medical literature since then.

In the same issue of the journal that carried the Relman report,[5] Slater and colleagues in Oklahoma City reported the successful isolation from blood cultures obtained from several immunocompromised patients of a novel gram-negative bacillus that had similar phenotypic features to *R quintana*,[6] and Perkocha and co-workers described the occurrence of bacillary peliosis hepatis in patients with AIDS.[7] A collaborative effort using molecular methods determined that the agent of bacillary angiomatosis and peliosis hepatis identified by DNA sequencing was identical to the cultivated microorganism identified in Oklahoma.[8] The new microorganism, now known as *Rochalimaea (Bartonella) henselae*, is fastidious and slow growing, and prolonged incubation is required to cultivate it.[9,10]

Subsequently, it was found that in several patients in San Francisco positive for the human immunodeficiency

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
PCR = polymerase chain reaction

virus who had typical bacillary angiomatosis associated with *B henselae*, their infection was instead caused by *R quintana*,[11] as shown by DNA sequence analysis of the 16S ribosomal gene of cultivated bacteria and those contained within biopsy specimens. Thus, the "old" agent of trench fever, a syndrome seen in immunocompetent patients, could also cause bacillary angiomatosis in immunocompromised patients. Later clinical studies on the West Coast suggest that these cases were probably part of a *B quintana* outbreak that occurred in the 1980s and that now appears to have subsided (J. E. Koehler, MA, MD, oral communication). At about the same time, it was reported that *B henselae* could also cause trench fever in persons with normal immune responses.[12] Thus, both closely related bacterial species caused trench fever in healthy adults and bacillary angiomatosis in immunocompromised patients, most of whom had AIDS.

Once *R henselae* had been cultivated, workers at the Centers for Disease Control (Atlanta, Georgia) developed a serologic test to determine whether cat-scratch disease might be caused by this microorganism, rather than by *A felis*. A seminal study demonstrated that an overwhelming proportion of patients with classical cat-scratch disease had antibodies to *R henselae*[13]; virtually none had antibodies to *A felis*. Currently there is convincing evidence from further serologic studies and molecular studies done on clinical specimens using PCR and to batches of skin test antigens for cat-scratch disease prepared from infected lymph node tissue that this disease is indeed caused by *B henselae*.[14] There is no evidence that either *A felis* or *B quintana* cause cat-scratch disease.

A close epidemiologic correlation between flea-infested cat exposure and the subsequent development of bacillary angiomatosis and cat-scratch disease has been documented.[15,16] Moreover, it has been discovered that 40% of asymptomatic cats have *B henselae* in their blood.[17,18] The application of PCR technology to the fleas obtained from these cats has clearly shown that fleas contain the microorganism and could serve as a transmitting vector.[17] Recent serologic studies on California cats have shown that most are seropositive for *B henselae*, suggesting the cat as the animal reservoir of infection in the community.[18]

Bartonella bacilliformis, the closest relative to the agents of bacillary angiomatosis, causes an overwhelming hemolytic anemia, called Oroya fever, in Peru in nonimmune persons exposed for the first time. In areas where the microorganism and its sandfly vector are endemic, infection is manifested by cutaneous lesions (verruga peruana) that are virtually identical with those caused by *B henselae* and *B quintana* in patients with AIDS and may be mistaken for Kaposi's sarcoma.

What implications do these tantalizing clues have for medicine and biology? For the first time, a bacterial organism has been shown to produce a typical granulomatous response in immunocompetent persons, whereas in immunocompromised patients, especially those with AIDS, the identical species and its closest relatives can elicit a peculiar and unique angiogenic response in skin, lymph nodes, liver, spleen, and many other organs. This astounding discovery clearly points to the importance of the host's immune response in determining the pathologic consequences of infection. It is likely that in immunodeficient patients, a specific *Bartonella* factor operates in the appropriate environmental milieu associated with defects in cellular immunity to promote excessive endothelial cell proliferation. Thus, if this novel bacterial factor(s) can be identified, it is likely to shed light on the mechanisms that underlie both benign and malignant endothelial cell proliferation typified by Kaposi's sarcoma. Although the putative infectious agent of Kaposi's sarcoma has recently been discovered,[19,20] the mechanisms by which this virus promotes endothelial cell tumor formation are obscure. Perhaps the ongoing research on *Bartonella* species infections can also elucidate the pathogenesis of Kaposi's sarcoma in the same immunocompromised host background.

We still lack specific information about other facets of *Bartonella* species infections, including the role of fleas in transmitting cat-scratch disease and bacillary angiomatosis, the nature of the animal reservoir of *B quintana*, and the identification of its presumed arthropod vector in the United States. Because many of the fascinating discoveries about *Bartonella* species infection were made possible through the application of molecular technology, future research to resolve these questions will certainly continue to exploit the marvelous sensitivity and specificity inherent in DNA.

REFERENCES

1. Wear DJ, Margileth AM, Hadfield TL, Fischer GW, Schlagel CJ, King FM: Cat scratch disease: A bacterial infection. Science 1983; 221:1403-1405

2. English CK, Wear DJ, Margileth AM, Lissner CR, Walsh GP: Cat-scratch disease—Isolation and culture of the bacterial agent. JAMA 1988; 259:1347-1352

3. Brenner DJ, Hollis DG, Moss CW, et al: Proposal of *Afipia* gen nov, with *Afipia felis* sp nov (formerly the cat scratch disease bacillus), *Afipia clevelandensis* sp nov (formerly the Cleveland Clinical Foundation strain), *Afipia broomeae* sp nov, and three unnamed genospecies. J Clin Microbiol 1991; 29:2450-2460

4. Stoler MH, Bonfiglio TA, Steigbigel RT, Pereira M: An atypical subcutaneous infection associated with acquired immune deficiency syndrome. Am J Clin Pathol 1983; 80:714-718

5. Relman DA, Loutit JS, Schmidt TM, Falkow S, Tompkins LS: The agent of bacillary angiomatosis—An approach to the identification of uncultured pathogens. N Engl J Med 1990; 323:1573-1580

6. Slater LN, Welch DF, Hensel D, Coody DW: A newly recognized fastidious gram-negative pathogen as a cause of fever and bacteremia. N Engl J Med 1990; 323:1587-1593

7. Perkocha LA, Geaghan SM, Yen TSB, et al: Clinical and pathological features of bacillary peliosis hepatis in association with human immunodeficiency virus infection. N Engl J Med 1990; 323:1581-1586

8. Relman DA, Falkow S, LeBoit PE, et al: The organism causing bacillary angiomatosis, peliosis hepatis, and fever and bacteremia in immunocompromised patients (Letter). N Engl J Med 1991; 324:1514

9. Regnery RL, Anderson BE, Clarridge JE 3d, Rodriguez-Barradas MC, Jones DC, Carr JH: Characterization of a novel *Rochalimaea* species, *R henselae* sp nov. isolated from blood of a febrile, human immunodeficiency virus-positive patient. J Clin Microbiol 1992; 30:265-274

10. Welch DF, Pickett DA, Slater LN, Steigerwalt AG, Brenner DJ: *Rochalimaea henselae* sp nov, a cause of septicemia, bacillary angiomatosis, and parenchymal bacillary peliosis. J Clin Microbiol 1992; 30:275-280

11. Koehler JE, Quinn FD, Berger TG, LeBoit PE, Tappero JW: Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. N Engl J Med 1992; 327:1625-1631

12. Lucey D, Dolan MJ, Moss CW, et al: Relapsing illness due to *Rochalimaea henselae* in immunocompetent hosts: Implication for therapy and new epidemiological associations. Clin Infect Dis 1992; 14:683-688

13. Regnery RL, Olson JG, Perkins BA, Bibb W: Serological response to '*Rochalimaea henselae*' antigen in suspected cat-scratch disease. Lancet 1992; 339:1443-1445

14. Dolan MJ, Wong MT, Regnery RL, et al: Syndrome of *Rochalimaea henselae* adenitis suggesting cat scratch disease. Ann Intern Med 1993; 118: 331-336

15. Tappero JW, Mohle-Boetani J, Koehler JE, et al: The epidemiology of bacillary angiomatosis and bacillary peliosis. JAMA 1993; 269:770-775

16. Zangwill KM, Hamilton DH, Perkins BA, et al: Cat scratch disease in Connecticut—Epidemiology, risk factors, and evaluation of a new diagnostic test. N Engl J Med 1993; 329:8-13

17. Koehler JE, Glaser CA, Tappero JW: *Rochalimaea henselae* infection: A new zoonosis with the domestic cat as reservoir. JAMA 1994; 271:531-535

18. Chomel BB, Abbott RC, Kasten RW, et al: *Bartonella henselae* prevalence in domestic cats in California: Risk factors and association between bacteremia and antibody titers. J Clin Microbiol 1995; 33:2445-2450

19. Chang Y, Cesarman E, Pessin MS, et al: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994; 266:1865-1869

20. Moore PS, Chang Y: Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 1995; 332:1181-1185

Conferences and Reviews

Initial Manifestation of Primary Hyperoxaluria Type I in Adults

Recognition, Diagnosis, and Management

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Primary hyperoxaluria type I may initially manifest as urolithiasis, renal insufficiency, or symptoms of systemic oxalosis. This hereditary disorder was fatal until effective therapies evolved during the past two decades. Difficulty in recognizing and diagnosing this disorder in adults is illustrated in a report of a patient eventually restored to good health by high-flux dialysis and combined renal and hepatic transplantation. I explore the molecular processes of the genetic defect and discuss clinical indicators of primary hyperoxaluria type I, manifestations of oxalosis, the pathogenesis of chronic oxalate nephropathy, and the diagnosis and management of this disease.

(Kuiper JJ: Initial manifestation of primary hyperoxaluria type I in adults—Recognition, diagnosis, and management. West J Med 1996; 164:42-53)

An autosomal recessive inborn error of glyoxylate metabolism, primary hyperoxaluria type I, can be cured by combined hepatic and renal transplantation.[1,2] The rarity of this disorder and its usual presentation in childhood ensure that physicians practicing adult medicine will be unlikely to be called on to diagnose the disorder in 1 of an estimated 65 new patients presenting annually in the United States.[3] The variability of initial clinical manifestations and the difficulty in accessing confirming studies for a patient whose condition is undiagnosed before renal failure develops complicate the management of this curable disorder. This review aids in the recognition, diagnosis, and treatment of patients who initially manifest primary hyperoxaluria type I as adults.*

Pathogenesis

Severe deficiency of enzyme activity catalyzing the transamination of glyoxylate to glycine (Figure 1) allows an overproduction of oxalate. In at least 75% of patients with primary hyperoxaluria type I, this overproduction is accompanied by excessive synthesis of glycolate (a valuable marker of this disorder).[4] Patients with primary hyperoxaluria generate oxalate at rates three to ten times normal.[5-7] Oxalate is not further metabolized; instead, renal excretion is required to prevent oxalosis, the accumulation of the highly insoluble calcium salt of oxalate in extrarenal tissues. Sustained hyperoxaluria leads to extreme supersaturation of urine with calcium oxalate, to calculi formation potentially complicated by urinary tract obstruction or infection, to renal tubulointerstitial injury and nephrocalcinosis, and to impaired renal function. In patients with this disorder, a decline in renal function from any cause forces the excretion of excessive oxalate by a diminishing number of nephrons, which may magnify oxalate-induced nephrotoxicity. A systemic accumulation of oxalate begins with glomerular filtration rates (GFRs) of less than 60 ml per minute.[5] With a decline in the GFR to 25 to 30 ml per minute or less, plasma oxalate levels rise dramatically, and generalized deposition of calcium oxalate accelerates.[5] Until the 1980s, the complications of urolithiasis, renal failure, and oxalosis led to death in 65% of these patients before age 5 years and in more than 80% before age 20.[1] The initial manifestation of the disease in adulthood has been unusual.

Investigations in the United Kingdom and the United States contributed greatly to the clinical and metabolic understanding of primary hyperoxaluria type I, which was first diagnosed in a living patient barely 40 years ago.[1,8] Elegant studies of the past eight years have defined the enzyme defect responsible for the disorder and its genetic and metabolic diversity.[4] This basic research has improved the diagnosis and treatment of this disorder dramatically. An extensively referenced review of its molecular processes has recently been published.[9]

Normally, to prevent the excessive production of relatively insoluble oxalate, a specific enzyme confined to hepatic peroxisomes, alanine-glyoxylate aminotransferase (AGT), effectively detoxifies glyoxylate by converting this metabolic intermediary to glycine. About

*See also the editorial by L. H. Smith, MD, "A Rare Twist to a Common Problem," on pages 83-84 of this issue.

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ABBREVIATIONS USED IN TEXT

AGT = alanine-glyoxylate aminotransferase
CT = computed tomographic
GFR = glomerular filtration rate

60% of patients with type I primary hyperoxaluria have no hepatic AGT activity. Immunochemical analyses of hepatic biopsy specimens suggest that the absence of AGT catalytic activity is usually accompanied by a loss of immunoreactivity of the inactive enzyme (group A, Table 1).[4] In a few patients, however (group B), the genetic mutation produces an immunologically detectable enzymatic protein devoid of AGT activity. About 40% of patients (group C) show considerable AGT activity, and many have AGT levels similar to those found in asymptomatic heterozygotes. The results of immunoelectron-microscopy indicate why adequate AGT catalytic activity results in an overproduction of oxalate: the enzyme is located in mitochondria instead of in peroxisomes, where glyoxylate can be metabolized efficiently. Thus, about 40% of patients with type I hyperoxaluria inherit a gene for active AGT that is functionally inert because it is located in the wrong organelle.

Pharmacologic dosing of the cofactor pyridoxine induces enough enzyme activity to shift the product of glyoxylate metabolism from oxalate to glycine in a small fraction of this subset of patients (4 of 24 group C patients in a series of 59 patients).[4] After cloning and sequencing the human AGT gene, point mutations were identified on chromosome 2 that are responsible for specific amino acid substitutions in the AGT molecule and that negate enzyme activity (group B), negate both enzyme activity and immunoreactivity (group A), or mistarget active enzyme to mitochondria (group C). A description of three patients with mutations that allow enzymatically inactive AGT to be located partially in mitochondria and partially in peroxisomal corelike structures implies that the phenotypic heterogeneity of this disorder is even more complex than Table 1 indicates.

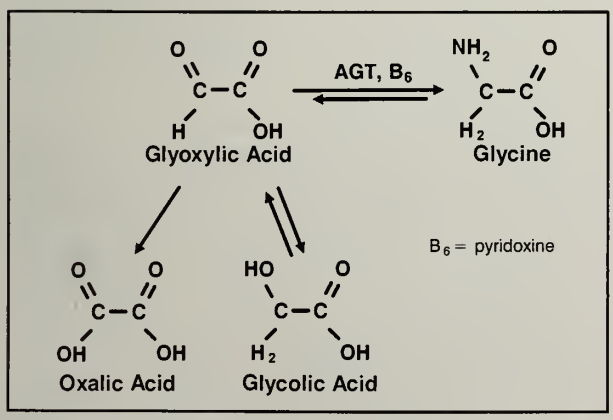

Figure 1.—The major pathways of glyoxylate metabolism are shown. Alanine-glyoxylate aminotransferase (AGT)-catalyzed transamination of glyoxylate to glycine and specific enzyme pathways converting glycolate and glycine to glyoxylate are confined to hepatic peroxisomes.

TABLE 1.—*Hepatic Alanine-Glyoxylate Aminotransferase (AGT) in Primary Hyperoxaluria Type I (PH-I)**

Group†	Approximate Percentage of PH-I Patients	Micraassayable AGT Activity	Immunareactive AGT Protein‡
A.....	40	–	–
B.....	20	–	+ (peroxisomes)
C.....	40	+	+ (mitochondria)

+ = present, – = absent

*From Danpure.[4]
†The designation of group A, B, and C patients facilitates discussion in the text.
‡The subcellular location of immunologically detectable AGT is indicated in parentheses.

Clinical Presentation

Typically, primary hyperoxaluria type I initially manifests in infancy or childhood as recurrent calcium oxalate urolithiasis, occasionally with insidious renal insufficiency or symptomatic oxalosis due to renal failure. Although 90% of patients with this disorder died within ten years of the development of the first symptom,[1] its diagnosis by pediatricians now allows prophylaxis that may preserve renal function and health.[3,8,10] A delay of diagnosis until adulthood despite substantial symptoms in childhood is relatively common, however.

Although unusual, the initial manifestation of symptoms in an adult aged 18 years or older was documented in 41 cases reported in the American and European biomedical literature in the past 40 years. Eight patients were in their fourth decade of life, one was in the fifth decade,[11] and five were in their sixth or seventh decade when the first symptom appeared.[4,12-14] The oldest patient appeared with arthralgia related to microcrystalline arthropathy, renal insufficiency, and nephrocalcinosis at age 66 years and died at age 71 after four years of dialysis.[14]

Report of a Case

The patient, a 45-year-old man, was seen in January 1991 because of morning nausea, a 2.3-kg (5-lb) weight loss, and muscle cramping of about five weeks. The medical history was uneventful except for episodes of dysuria and microscopic hematuria with negative culture results in November 1987 and again in February 1988. On both occasions, symptoms resolved without side effects during several days of treatment with the combination of sulfamethoxazole and trimethoprim. Follow-up urinalyses did not show hematuria. Studies done in April 1988 included a renal ultrasonogram, complete blood count, determinations of serum calcium, phosphorus, and parathyroid hormone levels, and an antinuclear antibody study, results for all of which were normal. A 24-hour urinary protein excretion was 0.05 grams (52 mg); serum creatinine levels ranged from 115 to 124 μmol per liter (1.3 to 1.4 mg per dl; versus 93 μmol per liter [1.05 mg per dl] in 1978). An extensive evaluation of symp-

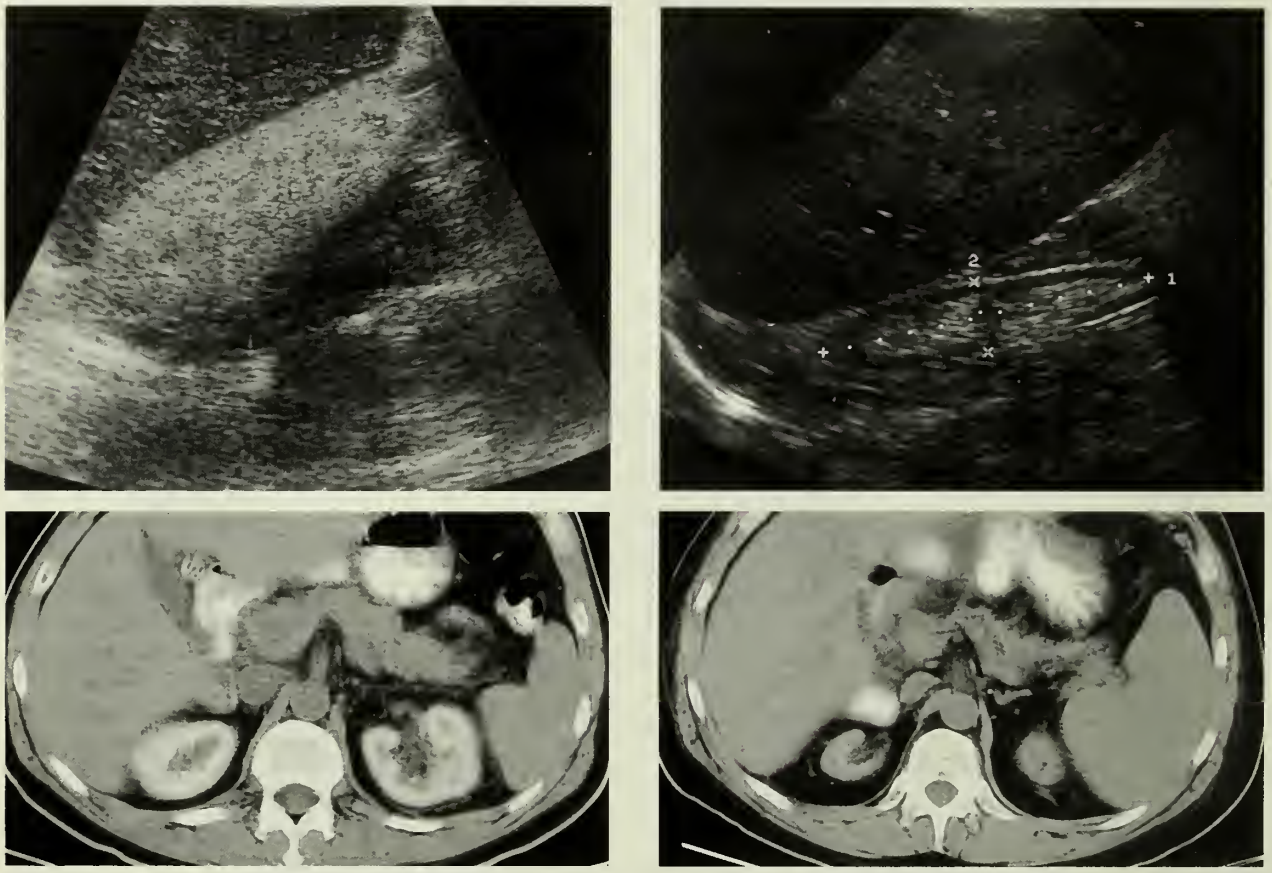

Figure 2.—Top left, A right renal ultrasonogram done in January 1991 showed the kidneys to be normal size and highly echogenic. **Top right,** A renal ultrasonogram done in December 1992 showed an atrophied right kidney with an echolucent cortex. **Bottom left,** Abdominal computed tomographic imaging without intravenous contrast was done in April 1991 and (**bottom right**) in August 1992. This imaging documented a reduction in renal cortical calcium oxalate deposition as well as renal atrophy after hepatic and renal transplantation in July 1991.

toms, medical history, habits, and possible toxic or infectious exposures proved unhelpful. The patient's three children and five siblings were healthy. His mother died at age 55 from complications of diabetes mellitus and hypertension and his father at age 84 of "old age." He was unaware of any family history of renal disease.

On physical examination, the results of which were normal except for azotemic fetor, the blood pressure was 130/90 mm of mercury with the patient either seated or standing. Laboratory data included the following: serum urea, 39.5 mmol per liter (blood urea nitrogen, 110 mg per dl); serum creatinine, 1,574 μmol per liter (17.8 mg per dl); mild metabolic acidosis; serum calcium, 2.32 mmol per liter (9.3 mg per dl); phosphorus, 2.62 mmol per liter (8.1 mg per dl); and hematocrit, 0.22 (21.9%). Urinalyses disclosed as many as 15 leukocytes and 20 erythrocytes per high-powered field, moderate calcium oxalate dihydrate crystalluria, and proteinuria (30 mg per dl; electrophoretically determined to be 16% albumin and 84% varied globulins without paraprotein). The kidneys on nephrosonography were found to be normal size and highly echogenic without corticomedullary demarcation or signs of obstruction (Figure 2). The results of other studies, including C3 and C4 serum complement, serum protein electrophoresis, liver function tests, chest x-ray films, and an electrocardiogram, were normal; the results of a tuberculin skin test and tests for antinuclear antibody, anti-DNA, and hepatitis B surface antigen were all negative. The intravenous administration of saline solution did not improve azotemic indices, prompting hemodialysis.

A surgical renal biopsy specimen four days after the recognition of nonoliguric azotemia in this clinically hydrated patient showed interstitial fibrosis and mononuclear cell infiltration (Figure 3). The pathologist recognized a few small crystalline deposits consistent with calcium oxalate scattered within tubular lumina and interstitium that were occasionally associated with small, multinucleated giant cells. Refractile crystalline material was not found, possibly because tissue was prepared in methacrylate resin instead of paraffin. Nonspecific, trace deposition of fluorescein-conjugated antisera within glomerular mesangium was not accompanied by immunofluorescence of tubular structures. Electron microscopy identified crystals with the needle-shaped morphologic features of calcium oxalate.

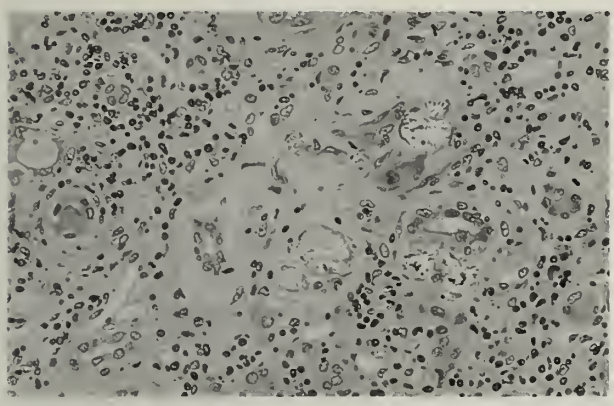

Figure 3.—A renal biopsy specimen shows chronic interstitial fibrosis and mononuclear cell infiltration. Crystals with morphologic features of calcium oxalate next to distorted tubules are sometimes surrounded by multinucleated giant cells (hematoxylin-eosin stain; original magnification, ×200).

Four urinalysis reports between 1974 and 1981 noted "4+ calcium oxalate crystals." Episodes of urethral discomfort and microscopic hematuria may have signaled the passage of small calculi. The diagnosis of primary hyperoxaluria type I was supported by later observations. The absence of diarrhea, steatorrhea, or an antecedent gastrointestinal surgical procedure and normal findings on gastric and small intestinal contrast radiography indicated that enteric hyperoxaluria was not present; the patient did not take vitamin C supplements, did not have exposure to ethylene glycol, and did not consume foods high in oxalate. Extreme, diffuse echogenicity and prominent radiographic and computed tomographic (CT) density of the normal-sized renal cortices suggested nephrocalcinosis. An abdominal x-ray film disclosed 3- and 5-mm calcific calculi in the lower pole of the left kidney.

The examination of a February 1991 biopsy specimen of the iliac crest showed numerous deposits of birefringent calcium oxalate crystals in trabecular bone (Figure 4). The patient's only sibling in the United States, a 52-year-old sister, recalled two episodes of urolithiasis that resolved spontaneously. Her 24-hour urinary oxalate level of 2.5 mmol (222 mg) (normal, <0.5 mmol [<45 mg]) and 24-hour urinary glycolate level of 3.6 mmol (268 mg) (upper limit of normal, 1.1 mmol [or 81 mg])[15] confirmed the presence of type I primary hyperoxaluria. This sister declined all efforts to evaluate and maintain renal function but remains well. The children and the four other siblings had normal renal function and 24-hour urinary oxalate levels.

As results accumulated, the patient returned to work and consumed a low-oxalate diet supplemented with pyridoxine, 300 mg daily. Anemia responded to the intravenous administration of erythropoietin and oral iron and folic acid supplements. In March 1991, metacarpal, metatarsal, and forearm bone pain, which was radiographically negative, prompted a progressive increase in the duration and frequency of high-efficiency hemodialysis (using a blood flow rate of 350 ml per minute and a 1.8-m^2 surface-area, polysulfone hollow-fiber dialyzer) that gradually relieved the bone pain. All symptoms other than minor hand pain resolved during high-flux dialysis for 3.5 hours a day and 5 days a week throughout May and June until combined hepatic and renal transplantation at the University of California, Los Angeles, Medical Center in July 1991. The absence of function of the liver transplant led to a second orthotopic liver transplantation the next day. Intensive dialysis continued during the first ten postoperative days before acute tubular necrosis of the cadaveric renal transplant resolved. A low-oxalate diet, 5 liters of daily fluid intake, and magnesium citrate supplementation (28 mEq 3 times a day) allowed continued urinary excretion of the previously accumulated oxalate burden (Figure 5) without calculus formation or renal allograft oxalate deposition. Comparison of results of CT and nephrosonographic studies obtained soon after the appearance of end-stage renal failure and again 14 to 18 months after transplantation revealed notable mobilization of calcium oxalate from native renal cortices (see Figure 2).

In June 1995, the serum creatinine level was a mean 177 μmol per liter (2.0 mg per dl). Hepatic function remained normal during combined cyclosporine-prednisone immunosuppression treatment, and the patient was clinically well.

Comment

Subtle symptoms and signs of urolithiasis preceded end-stage renal failure in a middle-aged man by four years and were recognized only in retrospect. Renal biopsy led to the correct diagnosis. Evidence of oxalosis in a bone biopsy specimen and the results of renal imaging studies supported the diagnosis of primary hyperoxaluria type I. Confirmation followed the diagnosis of the disorder in a sibling. The rapid evolution of symptoms of oxalosis while the patient received pyridoxine and conventional dialysis prompted successful symptom reversal by intensive high-flux hemodialysis and combined hepatic and renal transplantation. The removal of

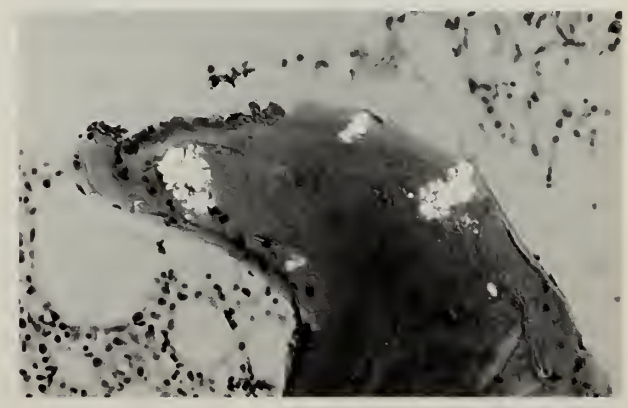

Figure 4.—An iliac bone biopsy specimen shows birefringent rosettes of calcium oxalate in trabeculae (hematoxylin-eosin stain; partially polarized light; original magnification, ×200).

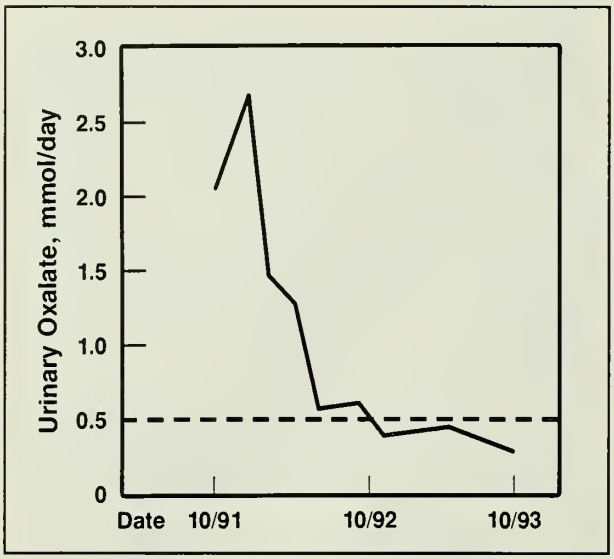

Figure 5.—The graph shows the patient's urinary oxalate excretion after transplantation. The broken line indicates the upper limit of normal (0.5 mmol/day).

oxalate in tissue required almost 1.5 years after the restoration of renal excretory capacity. Imaging study evidence of the dissolution of calcium oxalate in the renal cortex presumably mirrors dissolution in other sites, such as bone.

The early recognition of hyperoxaluria should receive major emphasis. Prompt detection and appropriate management of type I hyperoxaluria may prevent disabling consequences of oxalosis or the need for more elaborate therapy. If this patient had been referred to a nephrologist in April 1988, when renal function declined to 70% of normal, hyperoxaluria might have been considered as the cause of the episodic dysuria and microhematuria and of the incidental oxalate crystalluria. Considering the diagnosis of primary hyperoxaluria is the first obstacle. Obtaining expert guidance and confirming studies may present another problem.[11] Because this disorder is rare, few laboratories do reliable assays of plasma oxalate, plasma and urinary glycolate, or hepatic AGT activity. Numerous case reports illustrate a delay in the diagnosis despite recurrent oxalate calculi in childhood or oxalosis in siblings,[11] or until the development of oxalosis during continuous dialysis,[10,16-18] after renal transplantation,[19] or after pretransplantation nephrectomy.[20]

Clinical clues (including the manifestations of oxalosis) that should prompt the consideration of hyperoxaluria, the pathogenesis of chronic hyperoxaluric renal failure, diagnostic confirmation procedures, and the optimal management of primary hyperoxaluria are discussed next.

Recognition

Clinical indicators of type I primary hyperoxaluria include recurrent calcium oxalate urolithiasis, the most common indicator, tubulointerstitial nephropathy with nephrocalcinosis, which is a less frequent indicator, and eventually, symptomatic oxalosis.

Calcium Oxalate Urolithiasis

Because even a marginal elevation in urinary oxalate concentration promotes much greater supersaturation of calcium oxalate than similar increases in urinary calcium levels do, many advise measuring 24-hour urinary oxalate excretion in all patients with calcium oxalate calculi and certainly if calculi recur despite prophylaxis.[21] This policy ensures the identification of the rare patient with this disorder who presents with urolithiasis as an adult. The development of urolithiasis early in life characterizes primary hyperoxaluria. Factors that delay its initial manifestation until adulthood are poorly understood. The clinical investigation of renal insufficiency in an adult with evidence of diffuse cortical nephrocalcinosis or radiopaque calculi or a personal or family history of calcium-containing calculi in childhood should include measuring 24-hour urinary oxalate excretion. The diagnosis of primary hyperoxaluria should prompt the screening of all siblings—and possibly parents and children—for this recessive disorder. Heterozygous relatives excrete oxalate at rates observed in the normal population.

Urinalysis

Textbooks of laboratory diagnosis have commented on the frequent, incidental presence of bipyramidal (octahedral) calcium oxalate dihydrate crystalluria in normal persons, which excludes using the results of urinary sediment examination to predict hyperoxaluria.[1] In the case reported here, however, the notation of "4+ calcium oxalate crystals" on each of four otherwise routine urinalysis reports during ten years, when the serum creatinine level rose from 88 μmol per liter (1 mg per dl) to 124 μmol per liter (1.4 mg per dl), might have prompted a 24-hour urine oxalate determination and a review of the renal ultrasound study for signs of early nephrocalcinosis.

Tubulointerstitial Nephropathy–Nephrocalcinosis

Clinical or histologic evidence of a tubulointerstitial process of unknown cause should indicate the possibili-

TABLE 2.—*Features of Unexplained Renal Insufficiency or Failure Suggesting Primary Hyperoxaluria Type I (PH-I)*

Family history of PH-I or oxalosis
Personal or family history of calcium oxalate urolithiasis, especially in childhood
Cortical nephrocalcinosis with or without radiodense calculi
Any clinical manifestation of oxalosis, especially if confirmed by biopsy specimen examination
Bone or renal histologic examination shows more extensive oxalate deposition than anticipated in patients with non–PH-I ESRF
A reliable plasma oxalate level elevated beyond that expected in ESRF unrelated to PH-I

ESRF = end-stage renal failure

TABLE 3.—*Location and Clinical Manifestations of Oxalosis*

Tissue	*Clinical Manifestations*	*Supportive Study*	*Reference*
Bone, bone marrow	Osseous pain, spontaneous fracture, erythropoietin, resistance, pancytopenia, myelofibrosis, hypercalcemia, progressive edentia	Skeletal x-ray film, radioisotopic bone scan, bone biopsy	Canavese et al, 1990[16]; Breed et al, 1981[17]; Noël et al, 1989[19]; Day et al, 1986[22]; Toussaint et al, 1993[25]; Mathews et al, 1979[26]; Absy et al, 1991[27]; Moskow, 1989[28]
Synovium, tendon, cartilage	Acute and chronic arthropathy, chondrocalcinosis, bursitis, tendinitis	X-ray film, arthrocentesis, synovial fluid analysis, synovial biopsy	Verbruggen et al, 1989[14]; Moskow, 1989[28]; Hoffman et al, 1982[29]; Reginato et al, 1986[30]
Arteries, arterioles	Vasospasm, acrocyanosis, livedo reticularis, claudication, gangrene, angioaccess occlusion, vascular calcification	X-ray films, dermal biopsy, muscle biopsy	Watts et al, 1991[2]; Kay, 1993[11]; McDonald et al, 1989[20]; Day et al, 1986[22]; Winship et al, 1991[31]; Spiers et al, 1990[32]
Skin	Subcutaneous calcinotic nodules or masses, occasionally ulcerating	X-ray films, dermal biopsy	Day et al, 1986[22]; Moskow, 1989[28]; Scheinman et al, 1984[33]
Myocardium	Conduction defects, ventricular tachyarrhythmias, cardiomyopathy	Electrocardiogram, myocardial biopsy	Watts et al, 1991[2]; Kay, 1993[11]; Koten et al, 1965[13]; McDonald et al, 1989[20]; Absy, 1991[27]; Spiers et al, 1990[32]; Walls et al, 1969[34]
Retina	Mildly diminished vision, crystalline maculopathy	Ophthalmoscopy	Small et al, 1992[35]
Nervous system	Dysesthesia, weakness, symmetrical polyneuropathy, mononeuritis multiplex, optic atrophy	Peripheral nerve biopsy, ophthalmoscopy	Watts et al, 1991[2]; Scheinman et al, 1984[33]; Boquist et al, 1973[36]; Moorhead et al, 1975[37]

ty of primary hyperoxaluria type I if a patient has a history of calcium urolithiasis, nephrocalcinosis, or birefringent crystalline deposits in biopsy specimens. The results of urine protein electrophoresis in this patient suggested tubulointerstitial nephropathy, which was confirmed by renal biopsy.

The classic imaging feature of long-standing primary hyperoxaluria is diffuse cortical nephrocalcinosis with or without radiodense urinary tract calculi.[22,23] This finding is simulated only infrequently by the recovery from acute renal cortical necrosis, or rarely by chronic glomerulonephritis or sustained hypercalcemia, but the cortical calcifications are usually more linear or punctate than in primary hyperoxaluria, in which cortical density is diffuse.[23,24]

The clinical features of chronic renal insufficiency or failure that signal the presence of primary hyperoxaluria are listed in Table 2.

Oxalosis

Clinical manifestations of oxalosis (Table 3),* most frequent in bone, arteries, myocardium, skin, and synovia, may signal the presence of primary hyperoxaluria. The many case reports of patients with one or more frequently disabling manifestations of oxalosis attest to the importance of alertness to the possible clinical consequences of oxalate deposition in tissue. In primary hyperoxaluria, the varied findings of oxalosis were common before dialysis became available but are noted today—primarily in patients who enter renal failure with the condition undiagnosed or who receive standard dialysis.

In patients with progressive renal insufficiency unrelated to primary hyperoxaluria, the oxalate miscible pool and plasma levels are only mildly elevated even at a GFR of 8 to 10 ml per minute.[5-7,38] Tissue oxalate accumulation remains limited.[5] Conventional peritoneal dialysis and hemodialysis remove most normally generated oxalate if ascorbic acid supplements are limited to 100 mg daily.[6,39,40] Oxalosis associated with long-term dialytic therapy for renal failure from nonoxalotic causes tends to be an incidental histologic finding despite distinctly elevated plasma oxalate levels (15 to 18 times normal).[5-7,41] When clinically apparent in these patients, oxalate-induced synovitis,[29,30] cutaneous calcinosis,[30,42] oxalate osteopathy,[43] or complete heart block[41] are usually associated with prolonged dialysis (5 to 23 years), ascorbic acid supplementation (300 to 2,600 mg a day), high oxalate intake, or a combination of these factors.

Biopsy

Identifying birefringent calcium oxalate crystals in synovial fluid,[29,30] in myocardial tissue,[11,32] in the tunica media of arteries and arterioles, or occluding the lumina of small blood vessels on examination of biopsy speci-

*References 2, 11, 13, 14, 16, 17, 19, 20, 22, 25-37.

mens of specific tissues—skin and subcutaneous tissue,[11,31,32] muscle,[20] peripheral nerve,[37] synovium[29]—suggests the correct diagnosis of primary hyperoxaluria type I in patients who have end-stage renal failure of unknown cause. The longer the duration of renal failure before appropriate tissue is obtained through biopsy, the more pronounced is the histologic oxalosis.

Because the deposition of calcium oxalate crystals in trabecular bone is prominent in patients with primary hyperoxaluria in whom severe renal insufficiency is developing, the examination of percutaneous trephine bone biopsy specimens should suggest the correct diagnosis.[26] In contrast, the examination of an aspiration bone marrow biopsy specimen did not reveal oxalate deposition in a patient with the classic findings of oxalate-induced granulomatous myelofibrosis on examination of a later, formal bone biopsy specimen.[27] Others have noted the futility of examining aspiration bone marrow biopsy specimens in establishing the diagnosis of oxalosis.[36,44,45]

The efficacy of the examination of a renal biopsy specimen to diagnose this disorder as a cause of chronic renal insufficiency has not been documented. In the absence of superimposed oliguria, the biopsy specimen may reveal tubulointerstitial nephropathy without prominent oxalate crystal deposition. After dialysis is initiated in patients with end-stage renal failure, however, histologic examination of formalin-fixed, hematoxylin- and eosin-stained specimens of kidney should show large amounts of birefringent crystals within tubules.[33] Reflecting sustained overproduction and extremely high plasma levels of oxalate, the progressive deposition of calcium oxalate in these hypoperfused kidneys exceeds that incidentally noted in renal failure from other causes.[46] As shown by this patient, histologic evidence of renal oxalate deposition may be relatively minor in some patients with primary hyperoxaluria type 1 soon after the evolution of end-stage renal failure despite massive diffuse infiltration of the cortex by a form of calcium oxalate that is not doubly refractile on polarizing microscope examination. This situation may be clarified by considering the pathogenesis of chronic oxalate nephropathy.

Pathogenesis of Renal Failure in Primary Hyperoxaluria Type I

Possible mechanisms of renal injury in hyperoxaluria type I uncomplicated by calculous obstruction and pyelonephritis include crystalline obstruction of renal tubules, a rising level of plasma oxalate that complexes with the relatively concentrated intracellular calcium in renal tissue, or a toxic effect of hyperoxaluria on renal tubular epithelium.

The subtle intrarenal calcium oxalate precipitation in this patient is like that described in many patients with acute or chronic renal failure of any cause[41,47] and is dissimilar to the often-reported massive deposition in crystalline-occluded cortical convoluted tubules.[1,34,36] When clinical details are provided, proximal tubular obstruction by calcium oxalate rosettes in patients with this disorder accompanies acute neonatal renal failure,[44] dehydration and oliguria in children and adults,[12,13] or long-term dialysis with abundant evidence of systemic oxalosis.[34,36] Acute oliguria associated with contraction of the extracellular fluid volume or hypotension may allow the intratubular crystallization of calcium oxalate and may precipitate acute renal decompensation.

The chronic renal insufficiency in patients with sustained hyperoxaluria may be engendered by direct crystalline injury to renal tubular epithelium, initiating interstitial inflammation, giant cell formation, fibrosis, and nephrocalcinosis. The experimental production of mild chronic hyperoxaluria or moderate acute hyperoxaluria injures renal tubular epithelial cells in rats.[48] The absence or limited evidence of oxalate deposition despite interstitial nephritis has been documented in patients with primary hyperoxaluria type I before clinically important azotemia developed.[34,45,49] Light or electron microscopy has shown that intratubular crystals invade tubular cells and the interstitium, inducing patchy epithelial proliferation and interstitial inflammation.[36,50] Much less intraluminal oxalate crystal deposition has been noted in pyelonephritic kidneys than in noninfected, "nonobstructed," but anuric contralateral kidneys in two adult patients with type I hyperoxaluria who were dying of uremia.[13] This finding suggests that sustained diuresis and natriuresis of residual nephrons inhibit the intratubular precipitation of oxalate otherwise expected with extreme elevation of the plasma oxalate level.[45] Progressive deterioration of renal transplant function unrelated to rejection in patients with this disorder with only modest oxalate accumulation on the examination of specimens from serial renal biopsies suggests a direct toxic effect of massive hyperoxaluria in the initial months after transplantation.[33] Linear deposition of antitubular basement membrane antibody, severe tubulointerstitial nephropathy, and extensive intrarenal deposition of oxalate in a patient with enteric hyperoxaluria implicated oxalate damage to tubular epithelium, the release of tubular antigens, and immunologically mediated interstitial nephritis as the mechanism of renal failure in a 38-year-old patient 18 months after jejunoileal bypass.[51] Similar immunologic evidence is missing in patients with type I primary hyperoxaluria.

Diagnosis

Establishing the diagnosis of this disorder requires the demonstration of prominently elevated urinary or plasma levels of oxalate and evidence of an overproduction of glycolic acid, hepatic biopsy specimen documentation of deficient or mistargeted AGT, or in an appropriate setting (such as patients with nephrocalcinotic end-stage renal failure, biopsy evidence of oxalosis, or the exclusion of other hyperoxaluric causes), the confirmation of the disorder in a sibling (Table 4). Generally accepted values for oxalate and glycolate in various clinical circumstances reflect the results of sensitive assays done specifically to exclude interfering sub-

TABLE 4.—*Confirmation of Primary Hyperoxaluria Type I (PH-I) in End-Stage Renal Failure (ESRF)*

Hepatic biopsy—absent or severely deficient AGT activity; AGT maldistribution
Elevated plasma glycolate
With other features of PH-I–induced ESRF, hyperoxaluria, and glycolic-aciduria in a sibling

AGT = alanine-glyoxylate aminotransferase

stances such as ascorbic acid. Table 5 lists some of the laboratories that perform many of these special tests. The precise collection and handling of specimens is critical for reliable results.[3,6,38,52]

With adequate renal function, normal levels of urinary oxalate (<0.5 mmol [45 mg] per 1.73 m^2 in 24 hours) readily exclude the presence of primary hyperoxaluria. Patients with type I hyperoxaluria rarely have 24-hour oxalate excretion levels of less than 1.1 mmol (100 mg) per 1.73 m^2; mean excretory rates are 2.7 mmol (240 mg) and exceed 4.4 mmol (400 mg) in a few patients.[1,45] Acidifying 24-hour urine specimens during collection to a pH of less than 2.0 (by adding 20 ml of concentrated hydrochloric acid to the collection bottle) is mandatory to prevent the precipitation of oxalate salts and to limit the spontaneous nonenzymatic conversion of urinary ascorbate to oxalate.[3,52,53] If 24-hour urine collection proves impossible, simultaneous oxalate and creatinine determination by using a fasting second-voided morning urine specimen should allow the diagnosis of type I primary hyperoxaluria to be suspected or excluded.[54] A urinary oxalate:creatinine ratio exceeding 0.06 mmol:mmol (0.05 mg:mg) is characteristic of older children and adults with this disorder (most values exceed 0.125 mmol:mmol or 0.1 mg:mg).[3,15]

With mildly to moderately reduced renal function, patients continue to excrete oxalate in amounts approximating their high generation rates—1.2 to 4.5 mmol (108 to 405 mg) in 24 hours—have oxalate clearance as high as 2.7 times the corresponding creatinine clearance (implying clinically important proximal tubular secretion of the anion), and have a plasma oxalate level four to five times that of normal persons.[7,55] Urinary oxalate excretion progressively diminishes with GFRs of less than 40 ml per minute, but may remain sufficiently elevated to permit a suspicion of primary hyperoxaluria in patients with even moderately severe renal insufficiency. Limited glomerular filtration and tubular secretory capacity in renal failure prevent oxalate excretion determination from assisting in the diagnosis of the disorder with end-stage renal failure. Because plasma oxalate levels in these patients rise asymptotically with a decline in GFRs to less than 40 ml per minute, and particularly to less than 25 ml per minute, plasma oxalate and plasma oxalate:creatinine ratios are appreciably higher than they are in patients with similar degrees of chronic renal dysfunction unrelated to hyperoxaluria.[5-7,38,55]

In at least 75% of patients, an elevated 24-hour urinary glycolate level and especially a 24-hour urinary glycolate:creatinine ratio confirm the presence of primary hyperoxaluria type I.[1,4,5,15] A dramatically elevated plasma glycolate level in renal failure is present only in patients with this disorder.[38] A substantial decline in glycolate values with vitamin B_6 treatment confirms the presence of pyridoxine-responsive type I primary hyperoxaluria.

Patients with this disorder without evidence of excessive glycolate generation may require assays of hepatic AGT activity and subcellular location, the study of siblings, the repeated demonstration of reduced oxalate generation with pyridoxine supplementation, the exclusion of other causes of hyperoxaluria, or some combination of these methods to confirm the diagnosis.

Non-Type I Primary Hyperoxaluria

Excluding alternative causes of hyperoxaluria (Table 6) is usually straightforward. All are proven or possible contributors to oxalate urolithiasis; five must be considered in the differential diagnosis of oxalate nephropathy. Rare type II hyperoxaluria, documented in about 22 patients since 1968,[56] can be diagnosed by verifying excessive oxalate production and elevated urinary or plasma levels of L-glyceric acid or deficient activity of D-glycerate dehydrogenase in peripheral leukocytes or hepatic biopsy tissue. Urinary glycolate levels are normal or low in patients with type II primary hyperox-

TABLE 5.—*Laboratories Willing to Do Diagnostic Studies on Special Request*

Name, Address, and Telephone No. of Laboratory	*Assay*
D. A. Applegarth, PhD Biochemical Diseases Laboratory Dept of Pathology British Columbia Children's Hospital 4480 Oak St Vancouver, BC V6H3V4 (604) 875-2307	Hepatic biopsy: assay of AGT activity
Marguerite Hatch, PhD Div of Nephrology C 351, Med Sci 1 University of California Irvine, CA 92717 (714) 856-5562	Urinary and plasma oxalate
G. P. Kasidas, PhD Dept of Clinical Pathology University College and Middlesex School of Medicine Windeyer Bldg Cleveland St London W1P 6DP United Kingdom 071-636-8333	Hepatic biopsy: assay of AGT activity and subcellular location
Hibbard E. Williams, MD Office of the Dean, School of Medicine University of California Davis, CA 95616 (916) 752-0321	Urinary glycolate
David M. Wilson, MD Mayo Medical Laboratories Mayo Clinic Rochester, MN 55905 (507) 284-3019	Urinary and plasma oxalate, urinary and (?) plasma glycolate, and urinary L-glycerate

AGT = alanine-glyoxylate aminotransferase

TABLE 6.—*Differential Diagnosis of Hyperoxaluria*

Type	*Cause*
Primary hyperoxaluria	
Type I	AGT deficiency*
Type II	D-Glycerate dehydrogenase deficiency*
Type III	Hyperabsorptive
Secondary hyperoxaluria	Excessive oxalate intake
	Enteric hyperoxaluria*
	Ethylene glycol ingestion*
	Prostatectomy glycine irrigation
	Aspergillus species infection*
	Methoxyflurane anesthesia*
	Xylitol infusion*
	Piridoxilate therapy*
	Pyridoxine deficiency
	?Excessive ascorbic acid intake

AGT = alanine-glyoxylate aminotransferase

*Documented cause of oxalate nephropathy.

aluria. Hyperabsorptive type III hyperoxaluria reflects primary excessive intestinal absorption of divalent cations and oxalate without the recognizable structural features of the secondary forms of enteric hyperoxaluria. It responds to dietary oxalate restriction and long-term thiazide diuretic treatment.[57]

High dietary intake of oxalate in rhubarb, spinach, beet, parsley, pepper, peanut, chocolate, cocoa, and tea increases oxalate excretion and the risk of oxalate calculus formation.[52] Acute nephropathy accompanying oxalate poisoning from the ingestion of plants appears primarily ischemic.[58] Enteric hyperoxaluria from small intestinal disease, bypass surgery, or resection; chronic pancreatic or biliary tract disease; or complexing of dietary calcium by cellulose phosphate has caused calcium oxalate urolithiasis and oxalate-induced renal insufficiency.[51,53] Ethylene glycol remains a clinically important cause of acute oxalate nephropathy. Glycine absorption from the prostatic bed during transurethral prostatectomy occasionally induces clinically notable oxaluria.[59] The production of oxalic acid by severe infection with *Aspergillus* species has induced acute renal insufficiency histologically consistent with oxalate nephropathy.[60] Although methoxyflurane and xylitol cause hyperoxaluria, these compounds are no longer clinically available. Another hyperoxaluric agent, the vasodilator piridoxilate, has never been released in the United States.[61] Although proved experimentally, pyridoxine deficiency has not been clinically proved to cause substantial hyperoxaluria.[1,53,61] Megadoses of ascorbic acid may lead to laboratory evidence of hyperoxaluria.[52] Recent research in which the nonenzymatic conversion of urinary ascorbic acid to oxalate was controlled for and that used ion chromatography to accurately measure urinary oxalate excretion suggests that a supplementary dosage of oral vitamin C as high as 10 grams daily does not increase the urinary excretion of oxalate in normal subjects.[62]

Management

Pyridoxine Supplementation

Every patient should receive a therapeutic trial of pyridoxine during which urinary oxalate level, glycolate level, or both should be monitored (plasma glycolate level should be monitored if substantial renal impairment exists) (Table 7).[15,38,63] In patients with pyridoxine-responsive variants of type I hyperoxaluria, pyridoxine treatment often reduces the oxalate and glycolate levels to normal. Even a partial response benefits patients by limiting oxalate production through enhanced conversion of glyoxylate to glycine. Pyridoxine supplementation may elevate aminotransferase apoenzyme levels or may enhance the binding of vitamin B_6 to variants of AGT with low affinity for this essential cofactor.[9] Only a few patients with primary hyperoxaluria type I are sensitive to pyridoxine, however (7% in one series).[4] Although pharmacologic doses of 200 to 2,000 mg a day have been well tolerated,[8,19] severe sensory neuropathy within months of initiating vitamin B_6 supplementation mandates monitoring deep tendon reflexes and position and vibration senses.[64]

Preventing Urinary Oxalate Crystallization and Urolithiasis

Patients unresponsive to pyridoxine must adhere strictly to a program designed to allow maximal renal clearance of oxalate in as soluble a form as possible.[33] This program requires producing high daily volumes of diluted urine (which reduces the concentration and supersaturation of urinary calcium oxalate); avoiding extracellular fluid volume contraction, prostaglandin-inhibiting anti-inflammatory agents, and possible nephrotoxins[65,66]; and consuming inhibitors of urine calcium oxalate crystallization. With adequate renal function, adult daily doses of orthophosphate, 30 to 35 mg per kg of body weight[53,67]; magnesium oxide, 450 mg[53,63]; or sodium or potassium citrate, 40 to 60 mEq,[68,69] limited calcium oxalate urinary supersaturation, calculus formation, and at least for orthophosphate, renal insufficiency.[67] To minimize the incidence of diarrhea, initially small divided doses taken with meals are progressively increased to recommended levels. The patient in this report tolerated post-transplantation daily doses of 1 gram of magnesium and 84 mEq of citrate (as magnesium citrate) without side effects during the 17 months before urinary oxalate levels returned to normal. Serum magnesium levels remained normal. Percutaneous renal transplant biopsy at seven weeks disclosed a scant amount of oxalate proportional to the degree of renal insufficiency (serum creatinine level, 265 μmol per liter [3.0 mg per dl]). Renal biopsy 18 months after transplantation showed no evidence of oxalate crystals.

Although dietary oxalate provides a small fraction of the oxalate generated endogenously in patients with type I hyperoxaluria, such patients should avoid high-oxalate foods and ascorbic acid supplementation. Calcium intake should not be excessive. Because dietary calcium

TABLE 7.—*Management of Adult Patients With Primary Hyperoxaluria Type I*

Variable	*Treatment*
GFR ≥40 ml/minute	Pyridoxine trial High fluid intake; urine output >3 liters/day Crystallization inhibitors Neutral orthophosphate Magnesium Citrate Thiazide diuretic if patient has hypercalciuria Normal calcium level, low-oxalate diet without ascorbic acid supplements Avoid dehydration, possible nephrotoxins Prompt relief of urinary tract obstruction or infection Monitor renal function frequently
GFR <40 ml/minute	Continue measures listed above* Monitor renal function and plasma oxalate levels closely When GFR is 20-25 ml/minute, consider elective transplantation Initiate intensive hemodialysis when early ESRF results in systemic oxalate accumulation and before transplantation Avoid nephrectomy before ESRF

ESRF = end-stage renal failure, GFR = glomerular filtration rate

*Orthophosphate and magnesium are contraindicated.

forms complexes with gastrointestinal oxalate, which limits its absorption, documented hypercalciuria should be controlled by a thiazide diuretic instead of restricting calcium consumption below normal.[21,33] Caution is advised because of the capacity of thiazide diuretics to reduce the renal excretion of oxalate indirectly by contracting extracellular fluid volume and directly by inhibiting the tubular secretion of oxalate.[54] The optimal management of urinary calculi or infection includes a prompt recognition and use of kidney-preserving endoscopic and lithotriptic techniques and of non-nephrotoxic antibiotic agents. Extracorporeal shock-wave lithotripsy is relatively contraindicated.[70]

Preventing and Treating Oxalosis

The avoidance of disabling, possibly fatal oxalosis mandates close monitoring of renal function and considering transplantation before declining GFRs accelerate the systemic deposition of oxalate. Recent articles document arguments for various transplantation strategies: renal,[71] orthotopic hepatic,[72] and sequential[20] or simultaneous[2,10] orthotopic hepatic and renal transplantation. Heterotopic, auxiliary hepatic transplantation would not limit the excessive generation of oxalate by the native AGT-deficient liver.[10]

As demonstrated in this case and other reports, prolonged and frequent (even daily) hemodiafiltration or hemodialysis using high-flux membranes and blood flow has proved superior to conventional hemodialysis and peritoneal dialysis when dialytic support is required to limit oxalate accumulation and to deplete oxalate stores before transplantation.[7,40,63,73] The clearance of oxalate with a polysulfone or polyacrylonitrile membrane dialyzer averages 40% higher than the 82-to-89-ml-per-minute clearances produced by cellulosic membrane dialyzers of conventional size at the standard blood flow.[40,63] High-flux dialysis with the type of dialyzer used in the case described here produces oxalate clearance of about 180 ml per minute.[73] Because continuous ambulatory peritoneal dialysis and standard hemodialysis remove a mean 30% of the oxalate generated in primary hyperoxaluria type I, their sustained use is not recommended.[6,16,63] The longer the duration of conventional dialysis, the greater the oxalate burden and the less favorable the outcome of renal transplantation because of superimposed transplant oxalate nephropathy.[33]

The restoration of renal function by successful transplantation, followed by the provision of inhibitors of urinary calcium oxalate precipitation and by high fluid intake, permits the sustained clearance of accumulated oxalate.[33,71] The patient described in this review had urinary oxalate excretion as high as five to six times the upper limit of normal before levels returned to normal 17 months after transplantation. As the miscible oxalate pool is reduced, the dissolution of tissue oxalate resolves many manifestations of oxalosis: osteodystrophy,[10,22,25] complete heart block and cardiomyopathy,[2,20] neuropathy,[2] and cutaneous and subcutaneous deposits.[33] Imaging studies in this case document the mobilization of native renal cortical calcium oxalate deposits after the enzyme deficiency was corrected and adequate renal function was restored.

The diverse spectrum of acuity and age at onset of type I hyperoxaluria does not seem to be correlated with variations in AGT activity and subcellular location or the magnitude of hyperoxaluria.[4,18,45,71] To recognize the disorder early and initiate prophylaxis to reduce oxalate generation in some patients and provide optimal oxalate clearance in all patients remain the primary goals. Although intensive hemodialysis or renal or hepatic transplantation may prove optimal for selected patients in whom end-stage renal failure develops, combined hepatic and renal transplantation offers the best chance for cure. Improved inhibitors of urinary crystal growth, intestinal oxalate-complexing agents, and hepatic AGT gene transfer hold promise as future treatment methods.

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REFERENCES

1. Williams HE, Smith LH Jr: Primary hyperoxaluria, *In* Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS (Eds): The Metabolic Basis of Inherited Disease, 5th edition. New York, NY, McGraw-Hill, 1983, pp 204-228

2. Watts RWE, Morgan SH, Danpure CJ, et al: Combined hepatic and renal transplantation in primary hyperoxaluria type I—Clinical report of nine cases. Am J Med 1991; 90:179-188

3. Scheinman JI: Primary hyperoxaluria: Therapeutic strategies for the '90s (Editorial). Kidney Int 1991; 40:389-399

4. Danpure CJ: Molecular and clinical heterogeneity in primary hyperoxaluria type 1. Am J Kidney Dis 1991; 17:366-369

5. Morgan SH, Purkiss P, Watts RWE, Mansell MA: Oxalate dynamics in chronic renal failure: Comparison with normal subjects and patients with primary hyperoxaluria. Nephron 1987; 46:253-257

6. Marangella M, Petrarulo M, Cosseddu D, Vitale C, Linari F: Oxalate balance studies in patients on hemodialysis for type I primary hyperoxaluria. Am J Kidney Dis 1992; 19:546-553

7. Wilson DM, McCarthy JT: Plasma oxalate, fractional excretion of oxalate in primary hyperoxaluria before and after liver, kidney or liver/kidney transplantation (Abstr). J Am Soc Nephrol 1991; 2:261

8. Morgan SH, Watts RWE: Perspectives in the assessment and management of patients with primary hyperoxaluria type I. Adv Nephrol 1989; 18:95-106

9. Danpure CJ, Purdue PE: Primary hyperoxaluria, *In* Scriver CR, Beaudet AL, Sly WS, Valle D (Eds): The Metabolic and Molecular Bases of Inherited Disease, 7th edition. New York, NY, McGraw-Hill, 1995, pp 2385-2424

10. Watts RWE, Danpure CJ, De Pauw L, Toussaint C: Combined liver-kidney and isolated liver transplantation for primary hyperoxaluria type 1: The European experience—The European Study Group on Transplantation in Hyperoxaluria Type 1. Nephrol Dial Transplant 1991; 6:502-511

11. Kay J: Vascular occlusion and cardiac conduction disturbances in a patient undergoing peritoneal dialysis. Semin Dial 1993; 6:135-139

12. Chisholm GD, Heard BE: Oxalosis. Br J Surg 1962; 50:78-92

13. Koten JW, van Gastel C, Dorhout Mees EJ, Holleman LWJ, Schuiling RD: Two cases of primary oxalosis. J Clin Pathol 1965; 18:223-229

14. Verbruggen LA, Bourgain C, Verbeelen D: Late presentation and microcrystalline arthropathy in primary hyperoxaluria. Clin Exp Rheumatol 1989; 7:631-633

15. Wandzilak TR, Hagen LE, Hughes H, Sutton RAL, Smith LH, Williams HE: Quantitation of glycolate in urine by ion-chromatography. Kidney Int 1991; 39:765-770

16. Canavese C, Salomone M, Massara C, et al: Primary oxalosis mimicking hyperparathyroidism diagnosed after long-term hemodialysis. Am J Nephrol 1990; 10:344-349

17. Breed A, Chesney R, Friedman A, Gilbert E, Langer L, Lattoraca R: Oxalosis-induced bone disease: A complication of transplantation and prolonged survival in primary hyperoxaluria. J Bone Joint Surg (Am) 1981; 63:310-316

18. Skinner R, Tomson CRV, Tapson JS: Long term survival on haemodialysis in primary hyperoxaluria. Int J Artif Organs 1990; 13:412-415

19. Noël C, Sault M, Dhondt J, et al: Primary hyperoxaluria diagnosed after renal transplantation. J Nephrol 1989; 1:43-45

20. McDonald JC, Landreneau MD, Rohr MS, DeVault GA Jr: Reversal by liver transplantation of the complications of primary hyperoxaluria as well as the metabolic defect. N Engl J Med 1989; 321:1100-1103

21. Lemann J Jr: Composition of the diet and calcium kidney stones (Editorial). N Engl J Med 1993; 328:880-882

22. Day DL, Scheinman JI, Mahan J: Radiological aspects of primary hyperoxaluria. AJR Am J Roentgenol 1986; 146:395-401

23. Nemcek AA Jr, Ziewacz JT, Christiansen R, Conard FU: A 30-year-old woman with generalized skeletal pain. Invest Radiol 1987; 22:752-755

24. Arons WL, Christensen WR, Sosman MC: Nephrocalcinosis visible by x-ray associated with chronic glomerulonephritis. Ann Intern Med 1955; 42:260-282

25. Toussaint C, De Pauw L, Vienne A, et al: Radiological and histological improvement of oxalate osteopathy after combined liver-kidney transplantation in primary hyperoxaluria type 1. Am J Kidney Dis 1993; 21:54-63

26. Mathews M, Stauffer M, Cameron EC, Maloney N, Sherrard DJ: Bone biopsy to diagnose hyperoxaluria in patients with renal failure. Ann Intern Med 1979; 90:777-779

27. Absy MM: Atypical features of primary hyperoxaluria in end stage renal disease. Am J Nephrol 1991; 11:301-304

28. Moskow BS: Periodontal manifestations of hyperoxaluria and oxalosis. J Periodontol 1989; 60:271-278

29. Hoffman GS, Schumacher HR, Paul H, et al: Calcium oxalate microcrystalline-associated arthritis in end-stage renal disease. Ann Intern Med 1982; 97:36-42

30. Reginato AJ, Ferreiro Seoane JL, Barbazan Alvarez C, et al: Arthropathy and cutaneous calcinosis in hemodialysis oxalosis. Arthritis Rheum 1986; 29:1387-1396

31. Winship IM, Saxe NP, Hugel H: Primary oxalosis: An unusual cause of livedo reticularis. Clin Exp Dermatol 1991; 16:367-370

32. Spiers EM, Sanders DY, Omura EF: Clinical and histologic features of primary oxalosis. J Am Acad Dermatol 1990; 22(pt 2):952-956

33. Scheinman JI, Najarian JS, Mauer SM: Successful strategies for renal transplantation in primary oxalosis. Kidney Int 1984; 25:804-811

34. Walls J, Morley AR, Kerr DNS: Primary hyperoxaluria in adult siblings: With some observations on the role of regular haemodialysis therapy. Br J Urol 1969; 41:546-553

35. Small KW, Scheinman J, Klintworth GK: A clinicopathological study of ocular involvement in primary hyperoxaluria type I. Br J Ophthalmol 1992; 76:54-57

36. Boquist L, Lindqvist B, Östberg Y, Steen L: Primary oxalosis. Am J Med 1973; 54:673-681

37. Moorhead PJ, Cooper DJ, Timperley WR: Progressive peripheral neuropathy in patient with primary hyperoxaluria. Br Med J 1975; 2:312-313

38. Marangella M, Petrarulo M, Bianco O, Vitale C, Finocchiaro P, Linari F: Glycolate determination detects type I primary hyperoxaluria in dialysis patients. Kidney Int 1991; 39:149-154

39. Marangella M, Bagnis C, Bruno M, Petrarulo M, Gabella P, Linari F: Determinants of oxalate balance in patients on chronic peritoneal dialysis. Am J Kidney Dis 1993; 21:419-426

40. Marangella M, Petrarulo M, Mandolfo S, Vitale C, Cosseddu D, Linari F: Plasma profiles and dialysis kinetics of oxalate in patients receiving hemodialysis. Nephron 1992; 60:74-80

41. Salyer WR, Keren D: Oxalosis as a complication of chronic renal failure. Kidney Int 1973; 4:61-66

42. Abuelo JG, Schwartz ST, Reginato AJ: Cutaneous oxalosis after long-term hemodialysis. Arch Intern Med 1992; 152:1517-1520

43. Ott SM, Andress DL, Sherrard DJ: Bone oxalate in a long-term hemodialysis patient who ingested high doses of vitamin C. Am J Kidney Dis 1986; 8:450-454

44. Hockaday TDR, Clayton JE, Frederick EW, Smith LH Jr: Primary hyperoxaluria. Medicine (Baltimore) 1964; 43:315-345

45. Hall EG, Scowen EF, Watts RWE: Clinical manifestations of primary hyperoxaluria. Arch Dis Child 1960; 35:108-112

46. Murty MLN, Garg I, Date A, Jacob CK, Kirubakaran MG, Shastry JCM: Renal histology for the diagnosis of primary hyperoxaluria in patients with end-stage renal disease. Nephron 1989; 53:81-82

47. Fanger H, Esparza A: Crystals of calcium oxalate in kidneys in uremia. Am J Clin Pathol 1964; 41:597-603

48. Khan SR: Pathogenesis of oxalate urolithiasis: Lessons from experimental studies with rats. Am J Kidney Dis 1991; 17:398-401

49. Cochran M, Hodgkinson A, Zarembski PM, Anderson CK: Hyperoxaluria in adults. Br J Surg 1968; 55:121-128

50. Lieske JC, Spargo BH, Toback FG: Endocytosis of calcium oxalate crystals and proliferation of renal tubular epithelial cells in a patient with type 1 primary hyperoxaluria. J Urol 1992; 148:1517-1519

51. Zawada ET Jr, Johnston WH, Bergstein J: Chronic interstitial nephritis: Its occurrence with oxalosis and anti-tubular basement membrane antibodies after jejunoileal bypass. Arch Pathol Lab Med 1981; 105:379-383

52. Wandzilak TR, Williams HE: The hyperoxaluric syndromes. Endocrinol Metab Clin North Am 1990; 19:851-867

53. Smith LH: Hyperoxaluric states, *In* Coe FL, Favus MJ (Eds): Disorders of Bone and Mineral Metabolism. New York, NY, Raven Press, 1992, pp 707-727

54. Borsatti A: Calcium oxalate nephrolithiasis: Defective oxalate transport. Kidney Int 1991; 39:1283-1298

55. Kasidas GP, Nemat S, Rose GA: Plasma oxalate and creatinine and oxalate/creatinine clearance ratios in normal subjects and in primary hyperoxaluria: Evidence for renal hyperoxaluria. Clin Chim Acta 1990; 191:67-77

56. Chlebeck PT, Milliner DS, Smith LH: Long-term prognosis in primary hyperoxaluria type II (L-glyceric aciduria). Am J Kidney Dis 1994; 23:255-259

57. Yendt ER, Cohanim M: Absorptive hyperoxaluria: A new clinical entity—Successful treatment with hydrochlorothiazide. Clin Invest Med 1986; 9:44-50

58. Sanz P, Reig R: Clinical and pathological findings in fatal plant oxalosis: A review. Am J Forensic Med Pathol 1992; 13:342-345

59. Fitzpatrick JM, Kasidas GP, Rose GA: Hyperoxaluria following glycine irrigation for transurethral prostatectomy. Br J Urol 1981; 53:250-252

60. Nime FA, Hutchins GM: Oxalosis caused by aspergillus infection. Johns Hopkins Med J 1973; 133:183-194

61. Mousson C, Justrabo E, Rifle G, Sgro C, Chalopin JM, Gérard C: Pyridoxilate-induced oxalate nephropathy can lead to end-stage renal failure. Nephron 1993; 63:104-106

62. Wandzilak TR, D'Andre SD, Davis PA, Williams HE: Effect of high dose vitamin C on urinary oxalate levels. J Urol 1994; 151:834-837

63. Watts RWE: Treatment of renal failure in the primary hyperoxalurias (Editorial). Nephron 1990; 56:1-5

64. Schaumburg H, Kaplan J, Windebank A, et al: Sensory neuropathy from pyridoxine abuse: A new megavitamin syndrome. N Engl J Med 1983; 309:445-448

65. Irish AB, Doust B: Late presentation and development of nephrocalcinosis in primary hyperoxaluria. Aust N Z J Med 1992; 22:48-50

66. Grateau G, Grunfeld JP, Beurton D, Hannedouche T, Crosnier J: Post-surgical deterioration of renal function in primary hyperoxaluria. Nephrol Dial Transplant 1987; 1:261-264

67. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH: Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med 1994; 331:1553-1558

68. Lloveras JJ, Durand D, Dupre C, et al: Combined liver kidney transplantation in primary hyperoxaluria type I: Prevention of the recidive of calcium oxalate deposits in the renal graft. Clin Nephrol 1992; 38:128-131

69. Leumann E, Hoppe B, Neuhaus T: Management of primary hyperoxaluria: Efficacy of oral citrate administration. Pediatr Nephrol 1993; 7:207-211

70. Tan IL, Zonderland HM, Boeve ER: Oxalosis provoked by extracorporeal shock wave lithotripsy (Letter). Lancet 1994; 344:757-758

71. Katz A, Freese D, Danpure CJ, Scheinman JI, Mauer SM: Success of kidney transplantation in oxalosis is unrelated to residual hepatic enzyme activity. Kidney Int 1992; 42:1408-1411

72. Cochat P, Faure JL, Divry P, et al: Liver transplantation in primary hyperoxaluria type 1 (Letter). Lancet 1989; 1:1142-1143

73. Williams AW, Smith LH, Wilson DM, Milliner DS, Hart G, McCarthy JT: Removal of oxalate with hemodialysis in ESRD patients with primary hyperoxaluria (Abstr). J Am Soc Nephrol 1992; 3:690

Conferences and Reviews

New Developments in the Diagnosis and Treatment of Impotence

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New developments in the diagnosis and treatment of impotence or erectile dysfunction are increasingly based on better understanding of the erectile process. In 1978 it was thought that the failure of arterial inflow was the main cause of male erectile dysfunction. Emphasis was placed on methods of corpus cavernosal revascularization. In recent years, interest has shifted to abnormal cavernosal smooth muscle function. An understanding of the erectile process was greatly enhanced by intracavernosal administration of vasoactive agents in 1982 and, more recently, the use of prostaglandin E_1. These agents promote erection by causing smooth muscle to relax. The intracavernosal administration of vasoactive agents is now used in diagnosis and in therapy. Standard approaches to diagnosis and therapy still vary, but more rational steps are evolving. Considerable progress has been made in quantifying penile blood flow. Increasingly effective therapies are available for an estimated 10 million American men suffering from erectile dysfunction. Therapies include the use of drugs, administering vasoactive agents intracavernosally, vacuum constrictor devices, and vascular interventions in highly selected cases of arterial or venous disease. These procedures are being carefully reevaluated. Critical analysis of recent results suggests that about 7% of men are amenable to vascular interventions, with success rates approximating 70% when supplemental therapy is used.

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Although precise data are unavailable, an estimated 10 million American men are impotent, with the incidence increasing with age.[1] By age 65, 25% of men are impotent, and by age 80, about 80% of men are. Whereas impotence is primarily a dysfunctional vascular phenomenon, a number of mechanisms acting alone or interactively contribute to erectile failure. In this review, I consider current developments in its diagnosis and treatment.

History

In the past two decades, interest in the diagnosis and treatment of impotence has increased dramatically. Beginning with Leriche's 1923 observation that aortoiliac occlusion caused impotence due to failure of the perfusion of the corporal bodies,[2] surgeons became interested in the relationship between potency and cavernosal perfusion.[3] Aortic surgical interventions often produced impotence,[4] and in the 1970s, techniques were developed to minimize this complication.[5] It was also realized that vascular surgical procedures could be applied for corpus cavernosal revascularization.[6,7]

Consequently, corpus cavernosal revascularization was emphasized in the late 1970s and early 1980s. In 1982, however, it was found that erection could be stimulated by the intracorporal administration of the vasoactive agents papaverine and phentolamine.[8,9] This discovery helped to illuminate the processes of cavernosal smooth muscle function. Administering these agents intracorporally led to effective methods of testing and quantifying various aspects of erectile dysfunction as well as providing an important tool now used widely in diagnosis and treatment. Emphasis shifted from simple mechanistic efforts for increasing arterial inflow toward sophisticated investigations of corporal smooth muscle function. Important recent contributions include elaboration of the roles of nitric oxide and oxygen tension in normal erection and the delineation of mediators of corporal muscle contraction and relaxation.[10,11]

Physiology of Penile Erection

Penile erection results from a neurally mediated increase of arterial inflow into the corporal bodies along with a reduction or cessation of venous outflow. Recent findings support the idea that endothelially derived relaxant factor is involved in nonadrenergic, noncholinergic neural transmission, which leads to cavernosal smooth muscle relaxation required for normal erection.[10] Histochemically, nerve fibers positive for the reduced form of nicotinamide-adenine dinucleotide phosphate and diaphorase are found in human penile tissue, indicating nitric oxide synthase activity.[12] Other neurotrans-

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ABBREVIATIONS USED IN TEXT

CAOP = cavernosal artery occlusion pressure
DICC = dynamic infusion cavernosometry and cavernosography
NPT = nocturnal penile tumescence
PBI = penile brachial index
PG = prostaglandin

mitters such as vasoactive intestinal polypeptide and fibers positive for acetylcholinesterase are also present.

When the penis is flaccid, the corporal smooth muscle is contracted; contraction is due to a normally present overriding adrenergic tone.[13] With erection, smooth muscle relaxation occurs. Various other receptors are present in penile smooth muscle, including those responsive to vasoactive intestinal polypeptide, dopamine, histamine, prostaglandin (PG), and probably several other substances.

It has recently been reemphasized that the initiating event of penile erection is vasodilation.[11] With increased intracavernosal flow, an increased amount of oxygen is thought to stimulate nitric oxide synthesis by cavernosal nerves and endothelium. Cavernosal oxygenation promotes penile erection, whereas hypoxemia is inhibitory. Testosterone, in addition to its central effects, has been shown experimentally to stimulate nitric oxide synthase activity in corporal tissue,[14] enhancing sensitivity to cavernosal nerve stimulation in animals.

Hemodynamics and Diagnosis

The hemodynamics of the erectile process are shown in Figure 1. In flaccidity, the corporal smooth muscle and cavernosal arteries are contracted, and the emissary and pudendal veins are open. The intracavernosal pressure is equivalent to venous pressure; the blood in the intracavernosal spaces is desaturated. It is important to understand this physiologic process, which has recently been reviewed.[15] Current diagnostic methods such as dynamic infusion cavernosometry and cavernosography (DICC) are designed to measure penile pressure and flow changes. At low intracavernosal pressure in the flaccid state, a cavernosal or venous leak will always be detected radiographically.

In the next stage, the intracavernosal pressure increases to 80 to 90 mm of mercury synchronously with

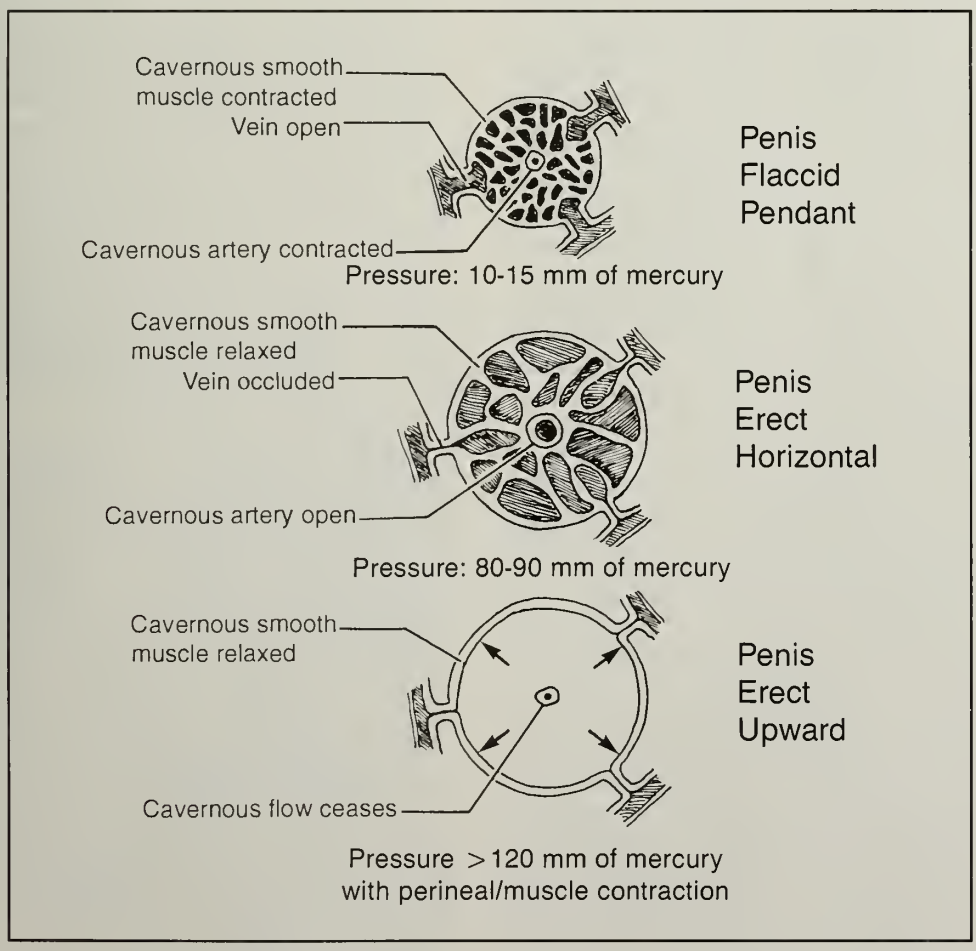

Figure 1.—The current theory of penile erection is illustrated. Three stages of erection are characterized by pressure measurements during dynamic infusion cavernosometry and cavernosography and after the intracavernosal administration of vasoactive agents. Note the vein occlusion in the second stage.

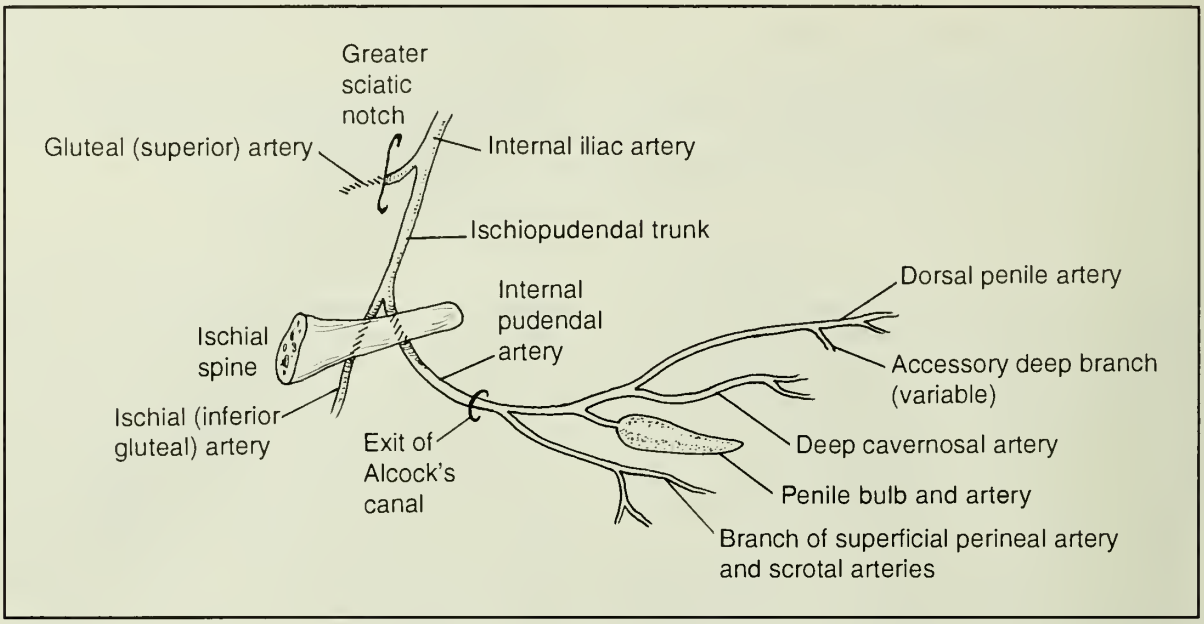

Figure 2.—A right oblique schematic is shown of the internal iliac artery and the pudendal artery and its branches. This view will be seen on highly selective angiography. Note the landmarks.

progressive smooth muscle relaxation, facilitating an increase in the arterial inflow. With full relaxation, the penile veins become obstructed due to the occluding action of the subalbugineal smooth muscle. A fully rigid erection on a vascular basis occurs with intracavernosal pressures of about 100 mm of mercury. The cavernosal artery occlusion pressure (CAOP) in full erection tends to equilibrate with the intracavernosal pressure while flow is markedly reduced. With pelvic muscular contraction, suprasystolic pressures are generated, maximum rigidity occurs, and cavernosal artery flow ceases transiently at this stage. For diagnostic purposes, flow changes can be measured at time intervals after the intracavernosal administration of vasoactive agents using duplex sonography.[16]

During DICC, the pressure at which the cavernosal artery flow ceases is detected by a Doppler probe placed at the penile base. This method uses artificial erection generated by a roller pump infusion of warm normal saline solution. The pressure at which the signal returns on pump flow reduction is taken as the CAOP. This value normally ranges from 80 to 90 mm of mercury, with a gradient of less than 30 mm of mercury as compared with a simultaneously obtained brachial pressure.[17,18]

The CAOP is an indirect assessment of the adequacy of arterial flow. Both large-vessel aortoiliac disease and abnormalities of the pudendal arterial supply (Figure 2) cause arteriogenic impotence. The flow to maintain erection is a measure of venous efflux provided complete smooth muscle relaxation has been obtained. The flow to maintain erection considered normal by our group is less than 40 ml per minute with pressure drops of less than 1 mm of mercury per second on flow cessation. The standardization of DICC depends on maximum muscular relaxation using the intracavernosal administration of vasoactive agents. With our method, 60 mg of papaverine hydrochloride and 2.5 mg of phentolamine were used. Readministration during DICC has recently been recommended to achieve maximal muscular relaxation and linear pressure-flow relationships.[19] An understanding of this process is also important for demonstrating penile arterial anatomy. When the intracavernosal administration of vasoactive agents produces full erection, radiographic artifacts due to cavernosal artery flow reduction occur. For penile artery visualization, the aim of this procedure is tumescence, not full erection; therefore, smaller doses must be used.

General Causes of Impotence

Although vasculogenic abnormalities are common, erectile failure is also caused by endocrine, metabolic, neurologic, and psychogenic factors. As can be seen from the physiology of erection, erectile failure is a vascular dysfunction. Some form of arterial inflow abnormality was associated with this complaint in about 45% of patients screened in a noninvasive vascular laboratory.[15] Endocrine causes of impotence were less common: 3% to 4% of patients demonstrated lowered testosterone levels. In screening more than 1,000 men, I found only 2 cases of pituitary prolactinomas. In both men, medical treatment was successful. This experience is similar to that in a study of 6,428 men.[20] The investigators also reported that specific endocrine disorders were uncommon. They found 20 cases of prolactinomas and noted that the restoration of a euthyroid state in 6 men failed to restore erectile function.

The most common associations with arteriogenic impotence are diabetes mellitus and the use of antihypertensive drugs. Men with diabetes can show neu-

ropathy when the vascular system appears to be normal by noninvasive testing. Overall, 28% of men screened neurologically for impotence exhibited one or more abnormalities in pudendal or tibial evoked potentials or bulbocavernosal reflex times.[21] The importance of these findings in contributing to impotence is difficult to assess, as some of these men also have existing vascular abnormalities. These techniques measure somatic nerve reflexes, but when present, abnormalities point to neurogenic deficits involving the genitourinary tract. Such men are often exquisitely sensitive to the intracavernosal administration of vasoactive drugs. The detection of nerve conduction deficits is to be a warning to avoid initially high doses of these agents, which could cause priapism.

Psychogenic problems are also often present in impotent men. Often anxiety and enhanced adrenergic tone are sufficient to override intracavernosally administered vasoactive agents in office settings. Cigarette smoking just before this procedure has been shown to inhibit erection in normal men after the administration of 80 mg of papaverine hydrochloride.[22] Despite limitations of the procedure, with the use of PGE_1 (up to 30 μg), it is a key diagnostic and therapeutic tool.[20,23] An erectile response after this procedure suggests that the arterial system is capable of delivering adequate flow and that corporal relaxation and venous closure are relatively functional.

Although neural or vascular abnormalities may be present, the observation of an effective erection after the administration of vasoactive agents also recommends its use as therapy. Such therapy can be effective regardless of the cause of erectile failure. It is important to better delineate possible etiologic factors as far as practicable in individual patients. The reasons for this are that occult aortic aneurysms and metabolic disorders such as uremia, diabetes mellitus, or other endocrinopathies can cause impotence.

Impotence due to nerve damage or possible arterial compromise often follows prostatic, rectal, or aortic operations. Radiation therapy for prostate cancer can cause late arterial inflow restriction. Arterial inflow compromise, in turn, causes venous leakage. Dynamic infusion cavernosometry and cavernosography alone, even with CAOP measurement, cannot with certainty suffice for the diagnosis of venous leakage. When both DICC and pudendal arteriography were used, 23% of men with normal noninvasive studies and suspected venous leakage were found to have associated arterial obstructive lesions.[24] These men (average age, 48.8 years) had lesions involving the pudendal and penile arteries. Table 1 summarizes the many mechanisms that can cause vasculogenic impotence.

TABLE 1.—*Factors in Vasculogenic Impotence*

Factor	*Probable Cause*
Cavernosal	
Arteriolar	Functional or anatomic; helicine vessel abnormalities; blood pressure medication
Fibrosis	Postpriapic; drug administration
Peyronie's disease	Deformity invading cavernosal smooth muscle; venous leakage through tunica albuginea
Refractory smooth muscle	Hormonal: prolactinemia, low testosterone level; blood pressure medication; metabolic: diabetes mellitus, uremia
Venous leakage	
Acquired	Abnormal tunica albuginea; traumatic lesions
Congenital	Isolated leakage from corpora cavernosum into the spongiosum
Arterial	
Aortoiliac atherosclerosis	
Steal due to external iliac disease	
Occlusive disease of pudendal arteries	Atherosclerotic
Occlusive disease of penile arteries	Atherosclerotic; idiopathic proliferative
Atheroembolization	

Approach to Diagnosis

Various noninvasive or invasive alternatives are used to investigate cases of erectile dysfunction. There is as yet no universally accepted approach. One approach begins with a limited patient goal-directed approach, depending on responsiveness or unresponsiveness to initial therapy.[25] If simple measures such as oral medications fail, more elaborate investigations are advised.[18,26] Should the intracavernosal administration of vasoactive agents fail or vacuum constrictor devices prove ineffective, workup would then progress to invasive delineations of abnormal physiology. Figure 3 illustrates such a sequence.

A diagnostic sequence based on noninvasive neurovascular screening can also be used before the office visit for a detailed history and physical examination.[27] Depending on the initial findings and a patient's desires, at this time, erectile function can be observed directly by administering PGE_1 intracavernosally. At the same time, blood specimens are obtained for prolactin, testosterone, glucose, and prostatic-specific antigen levels. As noted, initial noninvasive neurovascular testing can help determine the diagnostic category—that is, arteriogenic or neurogenic. This method of testing will be described further.

Noninvasive vascular testing in the flaccid penile state uses a penile brachial index (PBI), which is a ratio between the systolic pressure detected by a Doppler probe placed distal to an inflated 2.5-cm cuff.[27,28] The reappearance of Doppler signals in the dorsal artery branches just proximal to the glans signals reflow. This pressure is normally systemic. A PBI of 0.75 suggests that no major occlusion exists between the aorta and the distal measurement point. A PBI of less than 0.6 relates to major aortoiliac occlusion and almost always to erectile dysfunction. Penile pulse waves are then recorded using a pneumoplethysmographic cuff with a contained transducer. This procedure measures total pulsations of

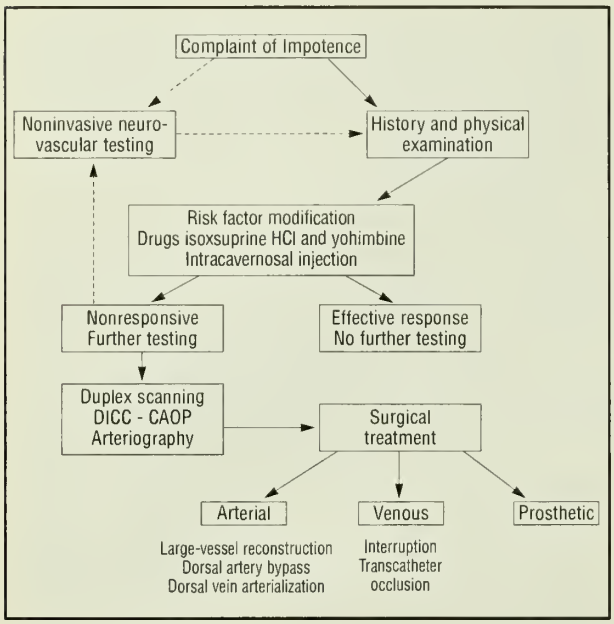

Figure 3.—A flow diagram is given showing a branched logic chain for the diagnosis and treatment of vasculogenic impotence. The dotted lines indicate optional pre-examination testing. See text. CAOP = cavernosal artery occlusion pressure, DICC = dynamic infusion cavernosometry and cavernosography, HCl = hydrochloride

all penile arteries as the cuff compresses the penile tissue at a mean arterial pressure. Variables recorded are crest time, waveform, and the presence or absence of a dicrotic notch on a polygraph with a chart speed of 25 mm per second and a sensitivity setting of 1. In normal men, the upstroke of the waveform is completed by 0.2 second (that is, a 5-mm space at a chart speed of 25 mm per second), and normal waveforms vary from 5 to 30 mm in height.

Although these noninvasive vascular laboratory tests help define arteriogenic impotence, impotence due to venous leak and other causes are not detected. In later studies, the sensitivity of these tests was shown to predict an abnormal arteriogram in 85% of cases.[18] Specificity—the percentage of true-negative tests—was 70%. The advantage of plethysmographic testing lies in the ability to define arteriogenic inflow problems before the office visit. These tests can be simply and inexpensively done by a vascular technologist. Neurologic testing uses pudendal evoked potentials, which have been shown to yield consistently reproducible values.[21,29,30]

Because many impotent patients have diabetes, pudendal responses are compared with spinal and cortical evoked responses from tibial nerve stimulation. Mean bulbocavernosal reflex times of 28.3 to 37.5 milliseconds compare with measured values from other laboratories.[30] Although this type of testing is more time-consuming and expensive than penile pressure and waveform analysis, it also provides important pretreatment data. This testing is useful in planning initial doses for the intracavernosal administration of vasoactive agents, in determining candidacy for further vascular studies, and in demonstrating the presence of neurologic disorders affecting the lower genitourinary tract.

These data facilitate a careful history and goal-directed physical examination. A history of a gradual onset of erectile failure in the absence of traumatic life events implies organicity. The complaint of claudication or physical findings of aortoiliac disease, aneurysmal or occlusive, suggest a diagnosis of arteriogenic impotence, supported by abnormalities seen on noninvasive arterial testing.[27] A recent and novel observation is that small aneurysms occasionally relate to an abrupt onset of impotence. This event due to atheroembolism can be documented by noninvasive studies.[31]

The presence of risk factors for atherosclerosis, mainly smoking, hyperlipidemia, hypertension, and diabetes, suggests a diagnosis of arteriogenic impotence, as does a history of pelvic or perineal trauma. The onset of impotence immediately after pelvic or arterial surgical therapy is critical. Finally, the presence of diabetes and any drug or alcohol use must be assessed.

Physical examination is often unrevealing when small-vessel arterial disease causes impotence. Leg-pulse deficits or femoral bruits suggest macroarterial disease. Sensory testing of extremities, perineum, and the glans occasionally detects neuropathy, but neurologic laboratory testing is much more sensitive. After examining the prostate and rectum, palpating the corporal bodies for Peyronie's plaques and the testes completes the examination. At this time, 10 to 30 μg of PGE_1 should be administered intracavernosally to observe the quality of erection achieved and to assess the response to therapy. The patient should remain in the office for at least an hour following this procedure.

Duplex sonography can be used at this point to scan the penile vessels after administering the vasoactive agent.[16,32] Control values for normal men are required for this procedure. For example, in middle-aged men after the administration of PGE_1 and visual sexual stimulation, a 70% increase in deep cavernosal arterial diameter and a systolic peak blood flow velocity in the range of 30 cm per second have been described as normal. Duplex scanning can also detect venous leakage with high diastolic flows, although here the data are less secure. Considerable interest exists in using this type of testing for selecting invasive procedures such as arteriography or DICC. My approach is to observe the quality of erection after increasing intracavernosal doses; when failure occurs or a Peyronie's plaque is found, duplex scanning is recommended. Ultrasonography can also scan for previously undetected abdominal aneurysms. Duplex scanning after the intracavernosal administration of a vasoactive agent, however, is more time-consuming than noninvasive vascular studies and requires a physician's presence before and after administering the agent.

A recent study shows the diagnostic problems of evaluating the veno-occlusive mechanism. Duplex scanning with the evaluation of end-diastolic flow showed

22% false-positive results.[33] When abnormalities of veno-occlusions were diagnosed using end-diastolic flow, subsequent nocturnal penile tumescence (NPT) monitoring proved to be normal in 8 of 37 men. The findings suggested anxiety in the clinical setting where duplex scanning was done. I do not use NPT monitoring routinely, but select this test when psychogenic impotence is likely or in cases of injury with continuing medicolegal problems. It is done optimally in a formal sleep laboratory with three nights of monitoring and the measurement of penile rigidity when erection occurs.[34] Normal penile rigidity or pressure is taken at 400 to 500 grams of axial buckling pressure. This test is both time-consuming and expensive, but it is important because a normal sleep erection virtually rules out organic erectile dysfunction. For screening purposes, a Rigiscan home NPT monitor is also employed. This may help by minimizing both the expense and anxiety in the clinical situation.

Treatment

At the outset, men with erectile dysfunction can be treated nonsurgically. Avoiding cigarette smoking, alcohol abuse, and drug use are first steps. Currently available oral drug therapy includes isoxsuprine hydrochloride, an α_1-adrenergic blocker; yohimbine hydrochloride; a presynaptic adrenergic-receptor agonist, trazodone hydrochloride; and vacuum constrictor devices. Four trials have been done with yohimbine with varying results, some patients showing improvement compared with those taking placebos.[35] The time to improvement has ranged from three days to three weeks, and this drug appears to be effective mainly when psychogenic factors are present. External vacuum devices have been reported to be effective in men for whom administering vasoactive agents intracavernosally had failed, as measured by patient rating and device return.[36] Although self-administering PGE_1 is common, a search continues for locally or intraurethrally applicable materials to avoid the need for intracavernosal administration.[37,38] It is now clear that orally administered drugs can induce erection and even cause priapism.[13] The mechanism of action of these drugs is likely an inactivation of α-adrenoceptor activity in cavernosal smooth muscle.

For patients with diabetes and men with neurovascular dysfunction, prosthetic devices can be recommended for those refractory to intracavernosal PGE_1 administration. The advantages and disadvantages of these devices have been summarized.[39] Over the past two decades, an estimated 250,000 men in the United States have received penile prostheses. Modern physiologic inflatable prostheses are self-contained with a built-in cylinder pump (a 2-piece device) or are three-piece devices. These consist of two cylinders connected to a scrotal pump without connectors because these were often the cause of failure. An outcome analysis was done from January 1984 to December 1993 of 328 implants, with follow-up data being obtained in 246, for a 75% follow-up rate. The infection rate for primary implants was 4.3%; for secondary implants, it was 10.8%. Depending on the prosthetic type, 82% to 90% of patients reported satisfactory prosthetic function, but only 71% of men were satisfied with the device. An interesting new development is the soft Subrini implant.[40,41] This is neither inflatable nor is it meant to provide rigidity. Rather, the device fills the cavernosal body to allow normal tumescence in naturally erotic situations.

Vascular Interventions

Were implants totally satisfactory, they would be more widely used. A functional vascular reconstruction is a more satisfactory option, but microvascular reconstructions of penile vessels and venous ligation procedures are being reassessed.[42] Skepticism exists regarding the many variants of penile revascularization or venous ablation because reported success rates range from 33% to 100%. Little life-table data exist to support these claims,[43] and no uniform methods of postoperative surveillance have been agreed on. Thus, in 1996 the true success rates of corporal revascularization or venoablative procedures are as yet unknown.[44] This situation is similar to the early period of coronary artery revascularization operations. Clearly, penile microvascular bypasses and venous interruption are evolving procedures. Better diagnostic criteria, techniques, and follow-up methods are needed.

Aortoiliac surgical techniques that perfuse the internal iliac arteries and spare autonomic nerves are less controversial.[15] Not only can iatrogenic impotence be avoided, but potency can be restored in 58% of men. In our recent report of ten years of experience with vascular intervention for impotence, men with the sole complaint of impotence underwent interventions for aortoiliac aneurysms or occlusive disease.[45] In these men, 58% resumed spontaneous function over follow-up periods ranging from 33 to 48 months; an additional 15% functioned with intracavernosally administered agents or vacuum constrictor devices. These men with aortoiliac disease averaged 61 years of age. In contrast, during the same period, men selected for microvascular procedures for penile artery bypass, deep dorsal vein arterialization, and venous ligation had an average age of 42 to 47.3 years. This age difference was statistically significant at a P value of .001 by analysis of variance. A significant difference between observed and expected frequencies of spontaneous erection was shown between those undergoing aortoiliac interventions and men having penile arterial or venous procedures. At 33 to 48 months after these operations, only 27% to 33% of men reported spontaneous erection. When intracavernosal administration of PGE_1 or vacuum constrictor devices were added, however, 72% to 77% reported functional erections that could not be previously obtained.

When the diagnostic screening sequences previously described were used[18,24,27] and patients with diabetes mellitus and those with hypertension were excluded, 6% to 7% among a group of 1,094 men became candidates for vascular interventions of differing types. A later analysis

was done of 1,145 cases of male impotence, and in a subset of 23 men with the primary complaint of impotence, 11 were found to have aneurysms and 12 had aortoiliac occlusions.[31] Noninvasive studies suggested that three probably had internal iliac or pudendal artery embolization that appeared to relate to the abrupt onset of impotence. About 1% of men with the complaint of impotence in this series have an associated aortic aneurysm. In men with risk factors such as smoking or hypertension and when abdominal palpation is inconclusive, ultrasound screening is useful to examine the aortoiliac segments. This small but important subgroup of older men demands careful workup because enlarging aneurysms are potentially lethal.

The Future

Most men with erectile dysfunction can be treated medically. The main modalities of therapy are the intracavernosal administration of PGE_1 and the use of vacuum constriction devices. The search for locally applicable or oral agents promises to be intense. Drug testing will rely on an enhanced knowledge of cavernosal smooth muscle function and will require more precise methods of objective documentation of results. The likely mechanisms of action of new agents will relate to an inhibition of α-adrenergic activity and the potentiation of other endogenous inhibitors of smooth muscle contraction.[13] These drugs might also be found to exert beneficial effects in peripheral vessels.

The process responsible for declining erectile function with age needs to be more clearly delineated. This process is not, as previously thought, a simple progression of arterial insufficiency and may not even be a manifestation of disease. Changes in the structure and function of aging cavernosal smooth muscle and neurotransmitters are as yet poorly documented.[46] Decreased nitric oxide synthase has been shown in cavernosal tissue of aging rats.[47] The local changes in penile tissue occur in conjunction with age-related decrements in nocturnal penile tumescence in frequency and degree, along with decreased sexual desire and coital frequency.[48]

The diagnosis and treatment of erectile dysfunction continue to advance. A well-disciplined diagnostic and therapeutic approach will rely less frequently on vascular interventions, except in the interesting subgroup of those with aortoiliac disease who require surgical intervention. Opportunities exist for improving prosthetic devices and refining choices and techniques of microvascular procedures. The treatment of men with erectile dysfunction requires a unique sensitivity to the needs and aspirations of each person, along with attention to details of diagnosis and therapy. Outcomes are satisfying as effective diagnostic methods and treatment have become better defined.

REFERENCES

1. Krane RJ, Goldstein I, Saenz de Tejada I: Impotence. N Engl J Med 1989; 321:1648-1659

2. Leriche R: Des oblitérations artérielle hautes (oblitération de la termination de l'aorte) comme cause de insufficances circulatoire des membres inferiurs (Abstr). Bull Mem Soc Chir 1923; 49:1404

3. Leriche R, Morel A: The syndrome of thrombotic obliteration of the aortic bifurcation. Ann Surg 1948; 127:193-206

4. May AG, DeWeese JA, Rob CG: Changes in sexual function following operation on the abdominal aorta. Surgery 1969; 65:41-47

5. DePalma RG, Levine SB, Feldman S: Preservation of erectile function after aortoiliac reconstruction. Arch Surg 1978; 113:958-962

6. DePalma RG, Kedia K, Persky L: Surgical options in the correction of vasculogenic impotence. Vasc Surg 1980; 14:92-102

7. Michal V, Kramář L, Pospíchal J, Hejel L: Gefässchirurgia erektiver Impotenz. Sex Med Sondertr 1976; 5:15-20

8. Virag R: Intracavernous injection of papaverine for erectile failure (Letter). Lancet 1982; 2:938

9. Brindley GS: Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis. Br J Pharmacol 1986; 87:495-500

10. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ: Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N Engl J Med 1992; 326:90-94

11. Azadzoi KM, Nehra A, Siroky MB: Effects of cavernosal hypoxia and oxygenation on penile erection (Abstr). Int J Impot Res 1994; 6(suppl 1):D4

12. Gopalakrishnakone P, Adaikan PG, Ponraj G, Ratnam SS: NADPH-diaphorase and VIP positive nerve fibres in human penile erectile tissue (Abstr). Int J Impot Res 1994; 6(suppl 1):A26

13. Adaikan PG: Physiopharmacological basis of treatment for erectile dysfunction (Abstr). Int J Impot Res 1994; 6(suppl 1):PL1

14. Brock GB, Zvara P, Sioufi R, Begin LR, Schipper HM: Nitric oxide synthase is testosterone dependent (Abstr). Int J Impot Res 1994; 6(suppl 1):D42

15. DePalma RG: Mechanisms of vasculogenic impotence, chap 32, *In* White RA, Hollier LA (Eds): Vascular Surgery—Basic Science and Clinical Correlations. Philadelphia, Pa, JB Lippincott, 1994, pp 359-368

16. Lue TF, Hricak H, Marich KW, Tanagho EA: Vasculogenic impotence evaluated by high-resolution ultrasonography and pulsed Doppler spectrum analysis. Radiology 1985; 155:777-781

17. Goldstein I: Vasculogenic impotence, its diagnosis and treatment, *In* de Vere White (Ed): Problems in Urology—Sexual Dysfunction. Philadelphia, Pa, JB Lippincott, 1987, pp 547-563

18. DePalma RG, Schwab FJ, Emsellem HA, Massarin E, Bergsrud D: Noninvasive assessment of impotence. Surg Clin North Am 1990; 70:119-132

19. Udelson D, Hatzichristou DG, Saenz de Tejada I, et al: A new methodology of pharmacocavernosometry which enables hemodynamic analysis under conditions of known corporal smooth muscle relaxation (Abstr). Int J Impot Res 1994; 6(suppl 1):A17

20. Keogh ET, Earle CM, Chew KK, et al: Medical management of impotence (Abstr). Int J Impot Res 1994; 6(suppl 1):S13

21. Emsellem HA, Bergsrud DW, DePalma RG, Edwards CM: Pudendal evoked potentials in the evaluation of impotence (Abstr). J Clin Neurophysiol 1988; 5:359

22. Glina S, Reichelt AC, Leão PP, Dos Reis JM: Impact of cigarette smoking on papaverine-induced erection. J Urol 1988; 140:523-524

23. Waldhauser M, Schramek P: Efficiency and side effects of prostaglandin E_1 in the treatment of erectile dysfunction. J Urol 1988; 140:525-527

24. DePalma RG, Dalton CM, Gomez CA, et al: Predictive value of a screening sequence for venogenic impotence. Impot Res 1992; 4:143-148

25. Lue TF: Impotence: A patients' goal-directed approach to treatment. World J Urol 1990; 8:67-74

26. DePalma RG: What constitutes an adequate impotence workup? World J Urol 1992; 10:157-158

27. DePalma RG, Emsellem HA, Edwards CM, et al: A screening sequence for vasculogenic impotence. J Vasc Surg 1987; 5:228-236

28. DePalma RG, Michal V: Point of view: Deja vu—again: Advantages and limitations of methods for assessing penile arterial flow. Urology 1990; 36:199-200

29. Opsomer RJ, Guerit JM, Wese FX, Van Cangh PJ: Pudendal cortical somatosensory evoked potentials. J Urol 1986; 135:1216-1218

30. Fisher-Santos BL, de Dues Viera AL, dos Santos ES: Bulbocavernosus reflex and evoked potentials in evidently normal males (Abstr). Int J Imp 1994; 6(suppl 1):A12

31. DePalma RG, Massarin E: Occult aortoiliac disease in men with primary complaint of erectile dysfunction. Int J Impot Res 1994; 6(suppl 1):A10

32. Lewis RW, King BF: Dynamic color Doppler sonography in the evaluation of penile erectile disorders. Int J Impot Res 1994; 6(suppl 1):A30

33. Mansour MOA: Anxiety mediated impotence misdiagnosed as venogenic impotence by color duplex scanning: A comparison with nocturnal tumescence monitoring. Int J Impot Res 1994; 6(suppl 1):A36

34. Ware JC, Kryger MH, Roth T, Dement WC (Eds): Chap 75, Principles and Practice of Sleep Medicine. Philadelphia, Pa, WB Saunders, 1989, pp 689-695

35. Yohimbine for male sexual dysfunction. Med Lett 1994; 36:115-116

36. Gould JE, Switters DM, Broderick GA, deVere White RW: External vacuum devices: A clinical comparison with pharmacologic erections. World J Urol 1992; 10:68-70

37. Cavallini G: Minoxidil plus capsaicine: An association of transcutaneous drugs for erection facilitation (Abstr). Int J Impot Res 1994; 6(suppl 1):D71

38. Canning JR, Marchese KR: Prostaglandin E as a topical agent for treatment of erectile dysfunction. Int J Impot Res 1994; 6(suppl 1):D82

39. Lewis RW: Prosthesis—Past, present, and future (Abstr). Int J Impot Res 1994; 6(suppl 1):S1

40. Austoni E, Fenici F, Mantovani F, et al: Functional role of complementary erection in soft silicone prosthetic penile implant (Abstr). Int J Impot Res 1994; 6(suppl 1):D127

41. Subrini L: Restoration of erectile function using soft penile implants (Abstr). Int J Impot Res 1994; 6(suppl 1):D137

42. Furlow WL: Vascular surgery in the treatment of impotence. Int J Impot Res 1994; 6(suppl 1):S8

43. Sohn M: Is there an indication for invasive diagnostic workup and vascular surgery in patients with erectile dysfunction? (Abstr) Int J Impot Res 1994; 6(suppl 1):S7

44. Sharlip I: A critical evaluation of short and long-term results of penile revascularization (Abstr). Int J Impot Res 1994; 6(suppl 1):S9

45. DePalma RG, Olding M, Yu GW, et al: Vascular interventions for impotence: Lessons learned. J Vasc Surg 1995; 21:576-585

46. Sohn M, Perber F, Melchert U, Sikora R, Bosshardt RJ, Handt S: Histological and ultrastructural workup of cavernous tissue from impotent patients (Abstr). Int J Impot Res 1994; 6(suppl 1):D141

47. Carrier S, Nagaraju P, Morgan DM, et al: The effect of aging on erectile function in the rat (Abstr). Int J Impot Res 1994; 6(suppl 1):D16

48. Schiavi RC, Schreiner-Engel P, Mandeli J, Schanzer H, Cohen E: Healthy aging and male sexual function. Am J Psychiatry 1990; 147:766-771

Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

Scott Votey, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association, and the summaries were prepared under the direction of Scott Votey, MD, and the panel.

Pediatric Fever Guidelines

At least two thirds of children visit a physician for an acute febrile illness before they are 3 years old. Respiratory, gastrointestinal, and urinary tract infections are most common in this age group. Occult bacteremia may occur in conjunction with any of these infections and most often occurs in children with fever without a known source and in those with otitis media. By definition, occult bacteremia is not characterized by any specific subjective or objective findings and is more frequent in children with higher temperatures. Since the introduction of the haemophilus b polysaccharide vaccine, the most frequent etiologic bacteria are *Streptococcus pneumoniae* and *Neisseria meningitidis*, accounting for about 90% and 4%, respectively, of the species identified in blood cultures. If a child with bacteremia is not given antimicrobial therapy, the overall risk of persistent fever is 42%, of persistent bacteremia 19%, and of meningitis 10%. The risk of meningitis occurring in children with *S pneumoniae* bacteremia managed as outpatients without antibiotic therapy is about 5%.

Occult urinary tract infections occur in about 7% of male infants younger than 6 months and 8% of female infants younger than 1 year with fever without a source. Only 80% of these infants will have greater than 5 leukocytes per high-power field in the urine sediment or a urine dipstick test positive for leukocyte esterase or nitrite. A Gram's stain of urine sediment will reveal bacteria in 99% of these infants. When occult urinary tract infections may be present, urine cultures should be done for all male infants younger than 6 months and all female infants younger than 1 year with fever without a source before antibiotics are empirically prescribed.

The relative risk of occult bacteremia is five times higher in children with a leukocyte count of 15×10^9 per liter or higher (≥15,000 per mm^3) (13% versus 2.6%). Therefore, the leukocyte count may be used to determine which children 3 to 36 months of age with a fever without a source should have a blood culture and antibiotic treatment. The use of the leukocyte count as a screening test will reduce by two thirds the number of patients in whom cultures are done and who are treated, but will result in 25% of children whose bacteremia goes undetected and untreated.

Blood cultures are recommended in children between 3 and 36 months of age with fever without a source (temperature, ≥39.0°C) if the leukocyte count is 15×10^9 per liter or higher. Blood cultures are not necessary when the presumptive diagnosis of a viral syndrome is supported by a benign clinical appearance and the presence of other family members or frequent contacts with an obvious viral syndrome.

The use of parenteral antibiotic therapy is a cost-effective approach to the management of children at risk of occult bacteremia. When the results of the blood or urine culture are reported as presumptively positive, the child should be reexamined. Children who are still febrile or who appear ill should have another blood culture and be admitted to a hospital for parenteral antibiotic therapy pending the results of these cultures. Children who are afebrile and appear well may be treated with the intravenous administration of an appropriate antibiotic or a ten-day course of oral antibiotics (or both).

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REFERENCES

Baraff LJ, Bass JW, Fleisher GR, et al: Practice guideline for the management of infants and children 0 to 36 months of age with fever without source—Agency for Health Care Policy and Research. Ann Emerg Med 1993; 22:1198-1210 [erratum published in Ann Emerg Med 1993; 22:1450]

Baraff LJ, Oslund S, Prather M: Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. Pediatrics 1993; 92:140-143

Lohr JA, Portilla MG, Geuder TG, Dunn ML, Dudley SM: Making a presumptive diagnosis of urinary tract infection by using a urinalysis performed in an on-site laboratory. J Pediatr 1993; 122:22-25

New Treatment of Atrial Fibrillation

THE EMERGENCY DEPARTMENT therapy for atrial fibrillation and in particular atrial fibrillation with concurrent congestive heart failure has undergone substantial change in the past few years. It is one of the most common arrhythmias emergency physicians encounter. Atrial fibrillation results in a chaotic and ineffectual contraction of the atrium that in turn produces irregular and frequently rapid ventricular contraction. Rapid, irregular ventricular contraction reduces effective diastolic filling and cardiac output. Atrial fibrillation and congestive heart failure often coexist, and one disorder can precipitate the other. Left atrial dilatation associated with congestive heart failure can result in atrial fibrillation. In patients with controlled heart failure, the onset of atrial fibrillation can reduce diastolic filling sufficiently to tip the patient into moderate or severe failure. The combination of rapid atrial fibrillation and congestive heart failure presents a management challenge.

Regardless of the cause of the fibrillation, the emergency management aim is usually the same: control the rate. Rate control improves diastolic filling and cardiac output. Digoxin has been used in the past for rate control in stable patients. But whereas digoxin has the advantage of being a positive inotrope, it has a slow onset of action. In an unstable patient, cardioversion has been the preferred option. Conversion to sinus rhythm in an emergency department is not usually the therapeutic goal for three reasons: First, in many patients the goal is not attainable. Second, after about three days of atrial fibrillation, an intra-atrial thrombus can form. Conversion to sinus rhythm without previous anticoagulation may result in thromboembolism. Third, rate control alone is sufficient to improve hemodynamics.

Rate control in patients with atrial fibrillation can be achieved rapidly with the calcium channel blockers, which act by slowing atrioventricular (AV) nodal conduction. Verapamil has been used to slow rapid atrial fibrillation but causes vasodilation and is a negative inotrope. Verapamil can precipitate deterioration or even hypotension in patients with congestive heart failure. Diltiazem is a newer calcium channel blocker that has substantial advantages over verapamil in the treatment of rapid atrial fibrillation. Diltiazem has similar effects on the AV node as verapamil, but has less negative inotropy and peripheral vasodilatory effects.

Several studies have confirmed the safety and efficacy of the use of diltiazem in patients with congestive heart failure with atrial fibrillation or flutter. Intravenous diltiazem can be safely used in most patients with rapid atrial fibrillation who are not hypotensive, and it has the advantage of a short duration of effect and relatively little negative inotropy. An initial bolus of 20 mg (or 0.25 mg per kg), followed by a continuous infusion (usually started at 10 mg per hour) often leads to smooth rate control in a time-frame suitable for emergency medicine. Studies of intravenous diltiazem use in patients with rapid atrial fibrillation and heart failure have shown improvements in cardiac output and stroke volume, with concomitant decreases in systolic blood pressure, systemic vascular resistance, and heart rate. The pulmonary capillary wedge pressure usually remains unchanged. Disadvantages to intravenous diltiazem use include a small but notable risk of hypotension, particularly in those patients with low cardiac outputs, and a relatively high cost—especially considering the need for a coronary care unit bed in a patient who might otherwise be admitted to a telemetry unit.

Combination therapy with the β-blocker esmolol hydrochloride and digoxin is another approach to achieving prompt rate control of atrial fibrillation in an emergency department. The premise of combination therapy is to use a rapidly acting agent to gain rate control while giving the patient digoxin, a slower but longer-acting agent. β-Blockers slow the ventricular response in atrial fibrillation but have the disadvantage of negative inotropy. Esmolol overcomes some of the limitations of other β-blockers because it is ultrashort-acting and therefore allows intravenous titration and rapid resolution of effect if hypotension ensues.

Further study validating the safety and efficacy of this approach will be necessary before it can be recommended for general use. Its use has been limited primarily to patients with thyrotoxicosis who are often refractory to more conventional means of treatment.

Digoxin can now be used in combination with intravenous magnesium for rapid rate control. An initial loading dose of 2 grams of magnesium sulfate (given over 15 minutes) is followed by 0.5 mg of digoxin intravenously and a continuous infusion of magnesium (1 gram per hour for 4 hours). This regimen achieves excellent rate control for most patients within two to four hours. Magnesium is relatively inexpensive and would be particularly attractive for those patients at risk for magnesium depletion, such as those with alcoholism or patients taking diuretics. There are, however, rare reports of long pauses when high doses (10 grams or more) are given. The use of magnesium is contraindicated in patients with renal insufficiency.

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REFERENCES

Ellenbogen KA, Dias VC, Cardello FP, et al: Safety and efficacy of intravenous diltiazem in atrial fibrillation or atrial flutter. Am J Cardiol 1995; 75:45-49

Goldberg IF, Lewis WR, Dias WR, Heywood JT, Pedersen VVR: Intravenous diltiazem for the treatment of patients with atrial fibrillation and moderate to severe heart failure. Am J Cardiol 1994; 74:884-889

Heywood JT, Graham B, Marais GE, Jutzy KR: Effects of intravenous diltiazem on rapid atrial fibrillation accompanied by congestive heart failure. Am J Cardiol 1991; 67:1150-1152

Shettigar UR, Toole JG, Appunn DO: Combined use of esmolol and digoxin in the acute treatment of atrial fibrillation or flutter. Am Heart J 1993; 126:368-374

Automobile Restraint Systems and Injury Prevention

DESPITE THE FACT THAT emergency physicians see people every day who have been injured in motor vehicle

accidents (MVAs), driving a car is becoming safer all the time. Fatality rates have been falling steadily for several decades due to many factors. Improvements have occurred in road design, education, and automobile design features that absorb the energy of collisions, such as collapsible steering columns, padded dashes, crumple zones, and laminated glass. None of these factors has had more effect on safety than restraint systems, which reduce the risk of ejection and lessen collisions between the occupant and the interior of the vehicle.

Seat belts have been available in automobiles since the 1950s, but did not achieve majority usage rates until states started imposing mandatory seat-belt use in the 1970s and 1980s. Currently 48 states have mandatory seat-belt laws, and all 50 states require child safety seats. Belt usage rates soared from about 10% in the 1970s to the current estimates of 67% nationwide and 83% in California. The National Highway Traffic Safety Administration estimates that a three-point seat belt alone reduces fatalities by 45%, and if an air bag is also present, there is an additional 10% reduction in fatalities. Drivers must be cautioned, however, that air bags used without seat belts are insufficient protection because they offer little protection in lateral collisions and do not prevent ejection. Since 1990 the requirements for United States-produced passenger cars include automatic restraints for the front seat (air bags or automatic belts) and three-point belts (lap and shoulder) for the back seat. By the 1998 model year, driver and front-seat-passenger air bags will be required on all new cars, along with manual lap and shoulder belts in the front and rear seats.

Seat belts and air bags alter the distribution of injuries produced in MVAs, and they even cause some injuries of their own. These injuries depend on the configuration of the belt system. For example, the classic "seat-belt syndrome" of a lumbar "chance" fracture and intestinal injury is caused by a lap belt riding up onto the abdomen of the occupant during sudden deceleration. Although air bags have caused some serious injuries such as ocular trauma and atrial rupture, most are less severe and include abrasions to the face, chest, and arms. Manufacturers are attempting to improve air bag materials so that they are lighter, more compact, and less abrasive.

Some problem areas persist for restraint systems. Children who are too large for protective child safety seats but too small to properly fit into seat belts designed for adults are at risk. Many manufacturers have introduced shoulder belts with adjustable anchors to combat this problem. The lateral collision is also a particular problem because there is less room to absorb the collision energy before it reaches the occupant(s).

No discussion of injury prevention in MVAs would be complete without mentioning the effects of alcohol use. Alcohol use is involved in 48% of fatal MVAs. A third of the drivers between the ages of 21 and 29 who are involved in a fatal accident are intoxicated. Although the number of alcohol-related fatalities in MVAs is slowly falling, large reductions in morbidity and mortality could be achieved by further reductions in the prevalence of drunk driving. Regardless of how effective restraint systems may become, the best way to prevent injuries is to prevent accidents.

We should be optimistic that advances in vehicle safety will continue to reduce the number and extent of injuries, and we should encourage our patients and their children to buckle up. We also need to continue to educate people not to drink and drive.

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REFERENCES

Accident Facts: 1993 Edition. Itasca, Ill, National Safety Council, 1993

Hendey G, Votey S: Injuries in restrained motor vehicle accident victims. Ann Emerg Med 1994; 24:77-84

Traffic Safety Facts 1994—Occupant Protection. US Dept of Transportation, National Highway Traffic Safety Administration, 1995

Viano D: Restraint effectiveness—Availability and use in fatal crashes: Implications to injury control. J Trauma 1995; 38:538-546

Use of Ultrashort-Acting Hypnotic Agents in Emergency Departments

EMERGENCY PHYSICIANS are faced with myriad reasons to use anesthetic agents in the course of practice. Often there is a need to do painful procedures in an emergency department for diagnosis and treatment, such as minor surgical or orthopedic procedures or endotracheal intubation. Sometimes the need is for sedation alone. A new approach to inducing unconsciousness rapidly in patients is the use of ultrashort-acting sedative-hypnotic agents, such as propofol, etomidate, and methohexital sodium. The ideal agent should have a quick onset of action, a duration sufficient for the procedure, and a rapid recovery profile with minimal side effects. All three drugs share similar features of rapid onset and recovery, but each produces some degree of cardiorespiratory depression. Careful monitoring of oxygenation, ventilation, and circulation is mandatory. These drugs alone do not provide analgesia or neuromuscular blockade, so other drugs should be administered for those purposes. The concomitant administration of narcotics and hypnotics may increase the incidence and severity of side effects.

Propofol is a phenol derivative prepared in a solution of 10% soybean oil and 1.2% egg phosphatide (Intralipid). Administering propofol intravenously (2.0 to 2.5 mg per kg of body weight) produces unconsciousness within 30 seconds. Lower doses can be used for sedation for various procedures, either by small boluses (0.2 to 0.4 mg per kg) or by infusion. Patients awaken more rapidly and completely than after other induction agents, usually in several minutes. These properties make propofol especially suitable for patients who are expected to be discharged after the procedure is completed. Propofol reduces the cerebral metabolic rate for oxygen and has been used to treat refractory status epilepticus. Cardiovascular depression, as evidenced by decreases in blood pressure (without a change in the heart rate), is greatest with the use of propofol and may be exaggerated

in patients who are hypovolemic, elderly, or those with compromised left ventricular function. The induction of unconsciousness may be associated with hypoventilation or apnea.

Etomidate is an imidazole derivative that also has a rapid onset of action and rapid recovery profile. It causes less cardiovascular and respiratory depression than propofol. After administration, the heart rate and cardiac output remain unchanged, but the mean arterial pressure may fall slightly due to a decrease in systemic vascular resistance. Etomidate is appropriately used for procedures such as endotracheal intubation and is given intravenously in a single induction dose of 0.3 mg per kg. Its use is well suited for patients with closed head injuries because it decreases the cerebral metabolic rate without causing substantial myocardial depression. Minor side effects in some patients include myoclonus and nausea and vomiting. Long-term use in critically ill patients has been associated with adrenocortical suppression and increased mortality. Plasma cortisol levels are reduced four to eight hours after a single induction dose. The implications of this short-term decrease are not well studied, but generally it does not produce serious complications.

Methohexital is a barbiturate that produces its effects through specific receptors in the γ-aminobutyrate system. An intravenous dose of 1 mg per kg produces unconsciousness in less than a minute. Recovery from unconsciousness is more rapid with methohexital than with other barbiturates, but is comparable to the other ultrashort-acting agents. It also can cause myocardial depression, and it lacks analgesic properties. Methohexital is the only agent that has been studied prospectively in emergency departments. Its use was found to be appropriate for many different procedures, although there was some variation in the reported success rate for each indication.

Propofol, etomidate, and methohexital are useful additions to the pharmacologic armamentarium for the care of patients in emergency departments. Physicians who use these agents must be skilled at caring for critically ill patients and be prepared to manage the complications of these drugs. Appropriate monitoring and airway management equipment must be available. Education and guidelines for use can help minimize adverse outcomes.

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REFERENCES

Levine RL: Pharmacology of intravenous sedatives and opioids in critically ill patients. Crit Care Clin 1994; 10:709-731

Proudfoot J: Analgesia, anesthesia, and conscious sedation. Emerg Med Clin North Am 1995; 13:357-379

Zink BJ, Darfler K, Salluzzo RF, Reilly KM: The efficacy and safety of methohexital in the emergency department. Ann Emerg Med 1991; 20:1293-1298

Asthma Advances and Controversies

THE MANAGEMENT OF acute asthma continues to evolve at a dizzying rate. As a consequence, many time-honored management practices have become questionable, resulting in considerable confusion. Whereas there continues to be no substitute for a good history, patients' estimation of the severity of their own illness has been shown to be disappointingly unreliable. In some series, as much as 60% of patients estimate their disease severity incorrectly, at least as verified by peak flows. Furthermore, although many of the classic signs of acute severe asthma help confirm severity, many of these signs—severe dyspnea, wheeze, accessory muscle use, inability to speak—are absent even in a patient in extremis. Thus, the absence of such signs cannot reliably rule out severe disease.

Peak flows, one of the few objective measurements available, are also imperfect predictors because they are effort dependent, do not consider attack duration (shorter episodes tend to respond more rapidly and completely to initial treatment), and are subject to individual variation. Consequently, patients must be coached to provide a maximum effort (best of 3), and results should be interpreted relative to normal values.

Pulse oximetry is currently enjoying a wave of popularity. Although it appears to be useful as a confirmatory tool at extremes of disease (arterial blood oxygen saturation [Sa_{O_2}] of <93% is considered severe and an Sa_{O_2} of >95% mild), its usefulness as a predictor of the need for hospital admission in moderately ill patients (Sa_{O_2}, 93% to 95%) is poor. Arterial blood gas measurements are only necessary in patients with severe disease, and chest x-ray films are only indicated when a particular complication—for example, pneumothorax, pneumonia—is suspected. Unfortunately, oxygen therapy has been given low priority in acute asthma. Most patients either get nothing or 2 liters by nasal cannula. In patients with acute severe asthma, this is clearly inappropriate because there is now good evidence that such patients die of acute hypoxia, and not arrhythmias, as previously thought.

Hydration in the past was widely touted, especially in children. Unfortunately, it has not been shown to affect pulmonary secretions in patients who have normal access to fluids, and many cases of pulmonary edema have been reported. Small children unable to access fluids may require hydration if objectively depleted.

Currently β-aerosols are an open-ended issue. It appears that the larger the dose and the more frequently it is administered, the greater the improvement without a corresponding increase in side effects.

In critically ill patients, it appears that continuous therapy is superior to the traditional intermittent regimens in both children and adults. Whereas there is an association between sicker patients using more drug and having increased mortality, any direct fault attributable to the β-aerosols seems to be due to an overreliance on them by patients and an underappreciation by physicians of the additional need for steroids. Perhaps β-agonists could be blamed for engendering a false sense of security (especially the longer-acting agents) because they provide symptomatic relief but do little to affect the underlying inflammatory process. Their appropriate use lies in treating acute episodes and should always be coupled with steroid

therapy in moderate to severe disease. β-Aerosols used in maintenance therapy are now recommended on an as-needed basis with a steroid or cromoglycate derivative given regularly. In patients with mild to moderate disease, administering these drugs through a metered-dose inhaler coupled with a holding chamber is equivalent to handheld or mask nebulization.

Parenteral adrenergic agents (terbutaline, epinephrine) are appropriate when maximal inhalational therapy fails because of severe unremitting airway obstruction, and these agents can be lifesaving. Parenteral theophylline, however, produces less bronchodilation than β-aerosols and increases the toxicity but not the efficacy of treatment; dosing is problematic. In addition, signs of minor toxicity (nausea and vomiting) do not necessarily precede those of major toxicity (seizures and arrhythmias), and life-threatening toxicity is not always predicted by the magnitude of the serum level and can be particularly difficult to treat. The use of parenteral theophylline in patients with acute asthma should no longer be controversial but rather should be considered obsolete.

Anticholinergic agents have proved tremendously effective in patients with chronic obstructive pulmonary disease, but this is generally not so in asthma. Usually greater benefit will be obtained from one more dose of a β-aerosol than adding an anticholinergic.

The aphorism "β-Aerosols treat the symptoms, steroids treat the disease" should always be kept in mind because asthma is an inflammatory disease. By modifying the immune response and increasing the responsiveness to β-agonists, steroids have particular benefit in decreasing the incidence of early recurrence and producing steady resolution of an acute exacerbation. The early use of parenteral steroids in emergency medicine has not been shown to reduce the incidence of admissions, but such therapy should be started in an emergency department. In addition, there is no advantage to the parenteral over the oral route of administration, unless the patient is unable to swallow. Magnesium, while safe and cheap, has been shown to be a mild, short-acting bronchodilator that offers little or no advantage over existing agents.

The use of mechanical ventilation should be avoided whenever possible, but it is the treatment of last resort. Once a patient has been intubated, oxygenated, paralyzed, and sedated, avoiding the occurrence of high peak airway pressures (>50 cm of water) is more important than that of hypercarbia. The former is associated with possibly fatal barotrauma whereas the latter can be managed with helium-oxygen mixtures. Helium-oxygen mixtures dramatically improve ventilation by decreasing resistance to flow and increasing carbon dioxide diffusion, among other effects. With asthma mortality rates still rising rapidly, the need for new approaches and technologies will continue. Patient education, prophylactic therapies, and earlier and more aggressive rescue treatment will form the basis of fighting this disturbing trend.

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REFERENCES

Idris AH, McDermott MF, Raucci JC, Morrabel A, McGorray S, Hendeles L: Emergency department treatment of severe asthma—Metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. Chest 1993; 103:665-672

Mullen M, Mullen B, Carey M: The association between β-agonist use and death from asthma—A meta-analytic integration of case-control studies. JAMA 1993; 270:1842-1845

Olshaker J, Jerrard D, Barish RA, Brandt G, Hooper F: The efficacy and safety of a continuous albuterol protocol for the treatment of acute adult asthma attacks. Am J Emerg Med 1993; 11:131-133

Dexamethasone Use in Croup

Croup, or acute viral laryngotracheobronchitis, is the most common cause of acute upper airway tract obstruction in children aged 6 months to 6 years, resulting in more than 20,000 hospital admissions annually; its incidence peaks in fall and winter. Croup's characteristic symptoms of loud barking cough, inspiratory stridor, retractions, and variable respiratory distress are usually mild and self-limited, but the spectrum of disease is great. Severe cases require admission to a hospital and, even rarely, intubation for the airway obstruction. Traditional management has included the use of humidified air, with supplemental oxygen and nebulized racemic epinephrine in patients with severe or refractory presentations. The effect of nebulized epinephrine disappears within two hours, however, giving little long-term benefit.

Corticosteroid administration has been suggested as a treatment adjunct in the management of croup. Theoretically, steroids may act to reduce subglottic edema and obstruction by decreasing capillary permeability and suppressing the local inflammatory reaction seen in laryngotracheobronchitis. Early studies that failed to show benefit have been criticized for inadequate steroid doses, inconsistent diagnostic criteria, failure to choose appropriate outcome measures, and other methodologic flaws. Two recent randomized, double-blinded, placebo-controlled trials using intramuscular dexamethasone, 0.6 mg per kg of body weight, for patients admitted to a hospital with croup have shown substantial improvements in patients' clinical indices as measured using a "croup score." This is a numeric assessment of the severity of respiratory symptoms, including inspiratory stridor, retractions, air entry, cyanosis, and level of consciousness. The croup scores were measured at 12 and 24 hours after the drug's administration. A meta-analysis of nine earlier published reports of 1,126 patients admitted to a hospital also concluded that parenteral steroid use had beneficial effects when compared with the effects of placebo. Most recently, patients treated through an emergency department have also been shown to have abatement of their clinical symptoms when given intramuscular dexamethasone as compared with placebo at 24 hours.

There are few contraindications to a single dose of parenteral corticosteroids. The use of a single intramuscular dose of 0.6 mg per kg of dexamethasone can now be considered standard therapy for most children presenting to an emergency department with moderate or severe

croup. The drug's long half-life of 36 to 54 hours allows for a single-dose regimen. Equipotent doses of another corticosteroid given orally, intravenously, or intramuscularly could also be expected to improve the outcome, but there are fewer data supporting various alternative regimens than those for single-dose dexamethasone given intramuscularly.

The role of corticosteroids in emergency department management of croup may expand in the future to include the use of nebulized corticosteroids. Nebulized budesonide, a synthetic glucocorticoid with relatively strong topical anti-inflammatory effects and low systemic activity has recently been shown to allow earlier discharge from an emergency department and a reduced rate of subsequent hospital admissions compared with placebo. An advantage of this therapy is its relatively rapid onset of effect; improvements can be seen as early as an hour after administration. The exact role of this new therapy for croup, however, remains to be determined.

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REFERENCES

Cruz MN, Stewart G, Rosenberg N: Use of dexamethasone in the outpatient management of acute laryngotracheitis. Pediatrics 1995; 96:220-223

Klassen TP, Feldman ME, Watters LK, et al: Nebulized budesonide for children with mild-to-moderate croup. N Engl J Med 1994; 331:285-289

Ledwith CA, Shea LM, Mauro RD: Safety and efficacy of nebulized racemic epinephrine in conjunction with oral dexamethasone and mist in the outpatient treatment of croup. Ann Emerg Med 1995; 25:331-337

Ottawa Ankle Decision Rules

THE REVISED OTTAWA ankle and foot rules are simple, specific guidelines used to assist physicians in deciding which blunt ankle and foot injuries require radiographs to exclude fracture. With less than 15% of ankle injuries resulting in substantial fracture, the objective is to eliminate radiographs in patients with injuries with a low probability of fracture. The rules assume a patient has a normal level of consciousness and no competing pain.

The criteria for ankle radiographs are pain in the malleolar area plus one or more of the following:

- Bone tenderness at the posterior edge of the distal 6 cm or tip of the lateral or medial malleolus, or
- Inability to bear weight both immediately after the injury and in the emergency department. Weight-bearing is defined as the ability to take four steps, two on each foot, with or without a limp.

The foot rules require pain in the midfoot plus one or more of the following:

- Bone tenderness at the base of the fifth metatarsal or navicular, or
- Inability to bear weight immediately after the injury and in the emergency department, as described above.

Large studies assessing these rules have shown a 100% sensitivity in identifying important fractures. Fractures are defined as bone fragments greater than 3 mm in breadth, a size that makes a patient a more likely candidate for rigid immobilization. The rules have safely allowed the reduction of the number of emergency department radiographs of the ankle and foot by close to 30%. This leads to a reduction in time spent in the emergency department, less cost for the visit by eliminating the radiographs, and less radiation exposure to patients. This has been accomplished without compromising patient satisfaction when an effort is made to educate the patient on why a radiograph is not necessary.

Some smaller studies have questioned the sensitivity of the rules when used by health care providers other than emergency department physicians. When residents, nurses, physician assistants, interns, and medical students are included, however, the sensitivity remains at more than 93%. A thorough education process is necessary, including access to simple diagrams to ensure accuracy in applying the rules.

Other criteria often empirically thought to add important data points, such as mechanism of injury, a "cracking" sound, ecchymosis, decreased range of motion, a positive drawer sign, soft-tissue tenderness, and proximal fibular tenderness, do not prove to be helpful in increasing the sensitivity of the selection criteria.

The ankle part of the study has been validated in a small group of children (68 patients with 14 fractures), aged 2 to 18 years, again finding 100% sensitivity and a 25% decrease in the number of radiographs.

The rules have not been validated for use in pregnant patients, but there is no reason to expect that they would not apply as effectively. Furthermore, a reduction in radiation exposure would seem to be a particular benefit of the rules in these patients.

These decision rules, while having a low specificity, do not miss important fractures. Despite their implementation, about 77% of ankle radiographs are still negative for fracture. The rules are substantially better at identifying patients with fractures than are physicians applying personal clinical criteria.

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REFERENCES

Chande VT: Decision rules for roentgenography of children with acute ankle injuries. Arch Pediatr Adolesc Med 1995; 149:255-258

Kerr L, Kelly AM, Grant J, et al: Failed validation of a clinical decision rule for the use of radiography in acute ankle injury. N Z Med J 1994; 107:294-295

Lucchesi GM, Jackson RE, Peacock WF, Cerasani C, Swor RA: Sensitivity of the Ottawa rules. Ann Emerg Med 1995; 26:1-5

Pigman EC, Klug RK, Sanford S, Jolly BT: Evaluation of the Ottawa clinical decision rules for the use of radiography in acute ankle and midfoot injuries in the emergency department: An independent site assessment. Ann Emerg Med 1994; 24:41-45

Stiell IG, Greenberg GH, McKnight RD, et al: Decision rules for the use of radiography in acute ankle injuries—Refinement and prospective validation. JAMA 1993; 269:1127-1132

Stiell IG, Greenberg GH, McKnight RD, Nair RC, McDowell I, Worthington JR: A study to develop clinical decision rules for the use of radiography in acute ankle injuries. Ann Emerg Med 1992; 21:384-390

Stiell IG, McKnight RD, Greenberg GH, et al: Implementation of the Ottawa ankle rules. JAMA 1994; 271:827-832

Preventive Care in Emergency Departments

EMERGENCY DEPARTMENTS (EDs) have emerged as vital possible sites for providing preventive care. Although the delivery of comprehensive preventive care in EDs is not practical, selected preventive care measures may be provided according to the needs and desires of patients served. Preventive care services that may be feasibly provided include immunizations, disease screening measures, injury prevention, and domestic violence screening.

The alarmingly low prevalence of complete immunization in pediatric populations has sparked the call for ED vaccination of children. In a study of preschool-aged children presenting to an urban ED, it was found that most patients were well enough to receive a vaccination. If vaccinations were offered to these children in the ED, immunization percentages would have increased 20% over a control group.

Elderly people likewise have suffered from deplorably low rates of immunization. Despite the Centers for Disease Control and Prevention's long-standing recommendation that everyone older than 65 receive a pneumococcal vaccination and yearly influenza vaccines, most older people fail to receive either vaccines. These recommended vaccines have minimal contraindications to administration, are paid for by Medicare, and can easily be provided for minor care of elderly patients in EDs.

Several disease screening and preventive care measures can be done in non-critically ill ED patients. Patients who are hypertensive at triage should have several blood pressures taken before discharge and, if elevated, should be referred for evaluation and possible treatment of hypertension. Using the CAGE* or other simple questionnaires, screening and referral for alcohol abuse can be accomplished in high-risk ED groups. More complex ED-centered screening programs for cervical cancer, hypercholesterolemia, syphilis, and human immunodeficiency virus have also been reported.

The provision of injury prevention information, such as car-seat and seat-belt guides, is a logical extension of after-care instructions for the millions of injured patients seen in EDs annually. Furthermore, using videotapes, pamphlets, and other educational materials, EDs can also educate noninjured patients and families about safety during their idle waiting room times. It was recently reported that few children treated for injuries receive documented injury prevention instruction.

The medical care entry point for many victims of violence, the ED is a critical site for preventive care intervention against domestic violence. One study showed that emergency physicians usually fail to recognize this problem. Although domestic violence was a reason for seeking care in the ED for 11.7% of women who had current male partners, the history of domestic violence was elicited in only 13% of these women. Tragically, 54.2% of all female ED patients interviewed reported a past occurrence of domestic violence. To improve the detection of this silent epidemic, ED physicians must be cognizant of its varied presentations. Incorporating questions regarding domestic violence in the history for all female ED patients is one possible method to achieve the goal of halting this epidemic.

Physicians have argued that costs, medical record difficulties, and lack of support staff time prohibit effective delivery of preventive care in the ED. They assert that ED preventive care may produce fragmented, sporadic primary care and bog down an already overloaded emergency medical system. Yet, many preventive care measures, such as those described herein, are simple, inexpensive, and do not require extensive record keeping. In light of substantial deficiencies in the overall delivery of preventive care in the United States, with a growing underclass that lacks access to any primary care, EDs must consider providing selected preventive care measures for non-critically ill patients as part of emergency care.

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*The CAGE test consists of the following questions:
Have you ever felt you should *C*ut down on your drinking?
Have people ever *A*nnoyed you by criticizing your drinking?
Have you ever felt bad or *G*uilty about your drinking?
Have you ever had a drink first thing in the morning to help yourself feel better (*E*ye-opener)?

REFERENCES

Abbott J, Johnson R, Koziol-McLain J, Lowenstein SR: Domestic violence against women: Incidence and prevalence in an emergency department population. JAMA 1995; 273:1763-1767

Bell LM, Lopez NI, Pinto-Martin J, et al: Potential impact of linking an emergency department and hospital-affiliated clinics to immunize pre-school-age children. Pediatrics 1994; 93:99-103

Dunn KA, Cline DM, Grant To, et al: Injury prevention instruction in the emergency department. Ann Emerg Med 1993; 22:1280-1285

Drug Interactions Associated With Terfenadine and Related Nonsedating Antihistamines

TERFENADINE (Seldane, Marion Merrell Dow) and astemizole (Hismanal, Janssen Pharmaceutical) are widely prescribed nonsedating antihistamines. Since 1990, when a case of torsades de pointes was reported in a patient using terfenadine and ketoconazole concomitantly, the potential for arrhythmias has been described when terfenadine or astemizole is used in excessive doses, in a patient with hepatic dysfunction, or when used concomitantly with ketoconazole or erythromycin. These drug-drug interactions have been implicated in a number of serious episodes, and recent research suggests that the incidence of concurrent prescribing may be increasing. This report summarizes the risk factors for ventricular arrhythmias developing with the use of terfenadine and other nonsedating antihistamines.

Terfenadine is rapidly and extensively metabolized by hepatic first-pass metabolism by a specific hepatic cytochrome P450 enzyme, CYP3A4, which converts terfenadine to its active metabolite, terfenadine carboxylate. After usual dosages, the parent compound cannot be

detected using standard assays. When unmetabolized terfenadine accumulates, however, it can induce a quinidine-like delay in cardiac repolarization that increases the risk of ventricular arrhythmias such as torsades de pointes. Consequently, any increase in the serum concentration of unmetabolized terfenadine increases the risk of QT prolongation and, therefore, serious cardiac arrhythmias.

Several clinical situations can lead to increased levels of unmetabolized terfenadine. In cases of acute overdose (as low as 360 mg) or in patients with impaired liver function, the hepatic metabolism of terfenadine may be overwhelmed. In addition, several medications can impair the metabolism of terfenadine. Because ketoconazole is an imidazole antifungal agent with potent inhibitory effects on cytochrome P450, unmetabolized terfenadine is detectable when these drugs are used concomitantly. In six healthy volunteers, the concomitant use of terfenadine and ketoconazole resulted in substantial increases in unmetabolized terfenadine and lengthening of the QT interval in all six subjects. The related compound, itraconazole, demonstrates the same inhibitory effect. By a similar mechanism, erythromycin blocks the metabolism of terfenadine, although probably to a somewhat lesser degree than does ketoconazole. Whereas other macrolide antibiotics such as troleandomycin and clarithromycin produce similar inhibitory effects, azithromycin may not undergo P450 oxidation and does not appear to interact with terfenadine in preliminary studies. Because cyclosporin is metabolized by the same hepatic cytochrome as terfenadine, agents that have been shown to inhibit cyclosporin metabolism may exhibit similar effects on terfenadine, including metronidazole, verapamil, diltiazem, and grapefruit juice. Finally, caution should be used when administering terfenadine concomitantly with agents that prolong the QT interval such as type 1A antiarrhythmics (quinidine sulfate, procainamide hydrochloride, and disopyramide phosphate), tricyclic antidepressants, sotalol hydrochloride, haloperidol (a structural analogue of terfenadine), thioridazine, probucol, cisapride, and pentamidine.

Astemizole is metabolized by the same cytochrome enzyme, and unmetabolized astemizole also demonstrates QT prolongation when serum concentrations are increased. Cases of adverse cardiovascular events have been reported when astemizole has been taken with erythromycin, ketoconazole, or itraconazole or at higher than the recommended dose. In general, any of the described conditions related to terfenadine toxicity should be considered for astemizole as well.

Loratadine (Claritin, Schering) and cetirizine hydrochloride (not yet approved by the Food and Drug Administration) are newer nonsedating antihistamines that have not shown cardiotoxic effects in preliminary studies. Although ketoconazole inhibits the metabolism of loratadine, no electrocardiographic effects were noted in 24 patients receiving concomitant therapy. Studies in humans and animals confirm the lack of cardiac effects in elevated dosages, and no ventricular arrhythmias associated with its use have been reported to date. Cetirizine hydrochloride also appears to be free of cardiotoxic effects in dosages as much as six times the recommended dose. Although these studies are preliminary, they suggest that these newer antihistamines may be safe alternatives when terfenadine or astemizole therapy is contraindicated.

Under certain circumstances, terfenadine and astemizole can induce life-threatening cardiac arrhythmias. The use of these agents should be avoided in patients with hepatic dysfunction and in patients receiving drugs that may inhibit their metabolism or prolong the QT interval, and these drugs should not be taken in excessive dosages. In addition, primary care and emergency physicians must consider these interactions in the examination of patients presenting with syncope or cardiac arrhythmias.

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REFERENCES

Honig PK, Wortham DC, Zamani K, Conner DP, Mullin JC, Cantilena LR: Terfenadine-ketoconazole interaction—Pharmacokinetic and electrocardiographic consequences. JAMA 1993; 269:1513-1518 [erratum published in JAMA 1993; 269:2088]

Smith SJ: Cardiovascular toxicity of antihistamines. Otolaryngol Head Neck Surg 1994; 111:348-354

Woosley RL, Chen Y, Freiman JP, Gillis RA: Mechanism of the cardiotoxic actions of terfenadine. JAMA 1993; 269:1532-1536

Zechnich AD, Hedges JR, Eiselt-Proteau D, Haxby D: Possible interactions with terfenadine or astemizole. West J Med 1994; 160:321-325

Role of Glucocorticosteroids in Treatment of Acute Spinal Cord Injury

THE ROLE OF GLUCOCORTICOSTEROIDS in the treatment of acute spinal cord injury has long been controversial. The mechanisms through which steroids exert their effects following spinal cord injury are still unknown. The leading theory is that steroids inhibit post-spinal cord injury lipid peroxidation and enhance recovery by inhibiting the injury-induced degenerative cascade that follows. Animal models of spinal cord injury treated with steroids in the early 1970s served as the basis for the National Acute Spinal Cord Injury Study (NASCIS I), published in 1985. This landmark study found no improvement in neurologic recovery in patients with acute spinal cord injury after the administration of methylprednisolone sodium succinate. Findings in animals suggesting that a higher dose of methylprednisolone may be beneficial led to NASCIS II, published in 1990.

In NASCIS II, patients with acute blunt spinal cord injury were randomly assigned to receive either methylprednisolone (30 mg per kg of body weight in an intravenous bolus, then 5.4 mg per kg per hour for 23 hours), naloxone, or placebo in a double-blind, prospective, multicenter clinical trial. Analysis of the entire study population did not show any statistically significant difference in the study arms. Subgroup stratification, however, found that the group receiving methylprednisolone in less than eight hours after injury showed significant

improvement in the neurologic score. The authors went on to conclude that these improved neurologic scores were "significant improvements in motor function and sensation." This resulted in the widespread use of high doses of methylprednisolone for acute spinal cord injury. Misinterpretation of this complex study has led to much confusion regarding eligibility criteria, benefits, and risks for patients with spinal cord injury who receive high doses of methylprednisolone.

NASCIS II relied on subgroup stratification to reveal any significant benefit of steroid use in acute spinal cord injury. Fundamental methodologic problems exist with subgroup stratification that is not followed by prospective validation of the results. Although subgroup stratification found high-dose steroids given within eight hours of injury improved neurologic scores, high-dose steroids given after eight hours actually caused significant worsening of neurologic scores. In addition, the authors themselves conclude that they were not able to translate the improvements in neurologic score into any improvement of functional status—quadriplegia improving to quadriparesis or paraplegia, and the like. NASCIS II excluded patients with serious coexisting life-threatening injuries and patients with spinal cord injury due to gunshot wounds; therefore, no conclusions regarding steroid use in these patients may be drawn. Finally, the safety profile of high-dose steroids remains in doubt. Whereas NASCIS I concluded that the use of steroids was associated with a statistically higher rate of infection, NASCIS II did not. A plausible explanation would be that NASCIS II lacked sufficient power to detect a significant difference in infection rates.

High-dose methylprednisolone—30 mg per kg of body weight given intravenously over 15 minutes, followed by a 45-minute rest period, then 5.4 mg per kg per hour for 23 hours—does appear to improve the neurologic state of patients with acute spinal cord injury if given within eight hours of injury. Based on available literature, if a patient is without life-threatening comorbidity and is suffering from blunt trauma-related spinal cord injury, administering high-dose methylprednisolone appears prudent. Whether this practice has a solid scientific basis awaits prospective validation of the results found in NASCIS II. The safety profile and how "improved neurologic scores" translate into functional neurologic recovery remain in doubt. Based on the current literature, the administration of high-dose methylprednisolone is not indicated and may be harmful if more than eight hours have elapsed since injury. There is no published scientific evidence to conclude that a patient with penetrating trauma-related spinal cord injury or with life-threatening comorbidity benefits from steroid therapy. Further studies on the effectiveness and safety profile of high-dose methylprednisolone are needed to clarify its role in acute spinal cord injury.

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REFERENCES

Galandiuk S, Raque G, Appel SH, Polk HC Jr: The two-edged sword of large-dose steroids for spinal cord trauma. Ann Surg 1993; 218:419-425

Prendergast MR, Saxe JM, Ledgerwood AM, Lucas CE, Lucas WF: Massive steroids do not reduce the zone of injury after penetrating spinal cord injury. J Trauma 1994; 37:576-580

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Alerts, Notices, and Case Reports

Lethal Ingestion of Chinese Herbal Tea Containing *Ch'an Su*

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Traditional Chinese herbal remedies are readily available from herb and grocery stores in most Chinese communities. Some of these products contain possibly toxic ingredients, are often imported into the United States illegally, and are associated with unproven claims of therapeutic benefit. This report describes the multifaceted investigation following the death of a young Chinese woman after she consumed a herbal remedy mixture prepared as a tea. A highly toxic ingredient in the tea was identified as secretions of the parotid and sebaceous glands of a toad (*Bufo bufo gargarizans* Cantor or *Bufo melanosticus* Schneider) that when used as a Chinese remedy is known as *ch'an su*. Although cases of toad-related poisonings have been described,[1-5] this is the first report of a death following the ingestion of a herbal remedy containing *ch'an su*. This investigation highlights the difficulties in identifying toxic components of herbal mixtures, the need for the cooperation of specialists of many fields to identify the causative agent(s) in these deaths, and the need for better controls over the use and availability of certain potent Chinese herbal remedies.

Report of a Case

The patient, a 25-year-old woman, presented to an emergency department because of a sudden onset of epigastric tenderness, several episodes of vomiting, and difficulty breathing that began immediately after she consumed tea brewed from a prescribed Chinese herbal remedy mixture. Abdominal pain was reported to have been present for a few days. The patient had a miscarriage about four months previously, and a few days before admission, she had been informed by her physician that she was again pregnant. She sought out a Chinese herbalist who prescribed a herbal remedy mixture to help her "sustain" her pregnancy. An in-store employee hired by the herbalist dispensed the remedy in two equal portions. After making one of the portions into a tea and drinking it for the first time that day, she immediately complained of perioral numbness. A few minutes after consuming slightly less than one "bowl" (about 100 ml) of the tea, she complained to her husband of nausea, then vomited and had increasing abdominal pain. She was immediately taken to the emergency department by her husband. She had no other relevant medical history.

On physical examination, the patient appeared listless but in no apparent distress; she had nausea but no diaphoresis. She was not cyanotic and had no signs of labored breathing. Her blood pressure was 120/80 mm of mercury, pulse rate 88 beats per minute, respirations 20 per minute, and temperature 36°C (96.8°F). The heartbeat was regular, the lungs were congested on expiration, and the abdomen was soft and nontender. The patient was drowsy but able to follow simple commands. The hemoglobin level was 125 grams per liter (12.5 grams per dl), the leukocyte count was 19.5×10^9 per liter (19,500 per mm^3), with 0.68 (68%) neutrophils, 0.28 (28%) lymphocytes, 0.03 (3%) monocytes, and 0.01 (1%) band forms. The serum sodium level was 133 mmol per liter; potassium, 3.9 mmol per liter; carbon dioxide content, 19 mmol per liter; and glucose, 8.4 mmol per liter (151 mg per dl). The blood urea nitrogen concentration and serum creatinine level were within normal limits. A portable x-ray film showed no evidence of cardiac enlargement or lung disease.

About 30 minutes after admission to the emergency department, the patient became pale, bradycardic, and progressively hypotensive. After the administration of atropine sulfate, sinus tachycardia developed and then cardiopulmonary arrest. During an hour-long resuscitative effort, the patient had a grand mal-type seizure. Despite all efforts, ventricular tachycardia developed, then intractable fibrillation. The patient died 2½ hours after she initially ingested the tea. The electrocardiogram was limited to a resuscitation rhythm strip.

A full autopsy was done less than nine hours after death. Gross findings were limited to a small amount of green-brown aspirated fluid in the proximal bronchi and a slightly enlarged uterus containing normal placental tissue consistent with a gestation of about one month. On microscopic examination, there was pronounced congestion of the viscera and minute foci of hepatic necrosis, all deemed consistent with vigorous resuscitation. Multiple

(Ko RJ, Greenwald MS, Loscutoff SM, et al: Lethal ingestion of Chinese herbal tea containing *ch'an su*. West J Med 1996; 164:71-75)

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cardiac sections, including of the conduction system, showed no inflammation or fibrosis.

Notably, investigating pathologists had abrupt, transient, severe rhinorrhea, coughing, and perioral numbness from handling the unused second portion of the herbal remedy mixture obtained from the family.

Methods

The tea was strongly suspected of causing the death after the postmortem examination failed to identify any natural disease process, including myocarditis or other cardiac abnormalities, drugs of abuse, common poisons, or therapeutic drugs in toxic amounts. A multidisciplinary approach was used to isolate and identify the suspected agent and to evaluate the public health ramifications of this case. Chinese herbalists with more than 20 years of experience were consulted to verify and translate the original prescription and to identify its individual components. Clinical toxicologic screening by the medical examiner's office was done on postmortem blood and urine specimens. Mouse bioassay and advanced analytical assays were done by the California Department of Health Services (DHS) and the United States Department of Agriculture on specimens of the tea and the unused portion of the herbal mixture. Public health investigators from DHS reviewed the cases of other deaths in the community that, in hindsight, might be attributed to undiagnosed poisoning by herbal remedies.

TABLE 1.—*Preparation of Materials* and Results of Mouse Bioassay of a Chinese Herbal Remedy*

Material	Result: Time to Death, min:sec	Result: Dilution
Brewed tea (A)†	Death 3:45-4:45	No
Dilution of A	Death 37:50	1:9 H_2O
Tap water boiled in patient's teapot	No death	No
Unused herbal remedy mixture brewed by authors (B)	Death 2:30	No
Dilution of B	Death 19:59	1:10 H_2O
Component of B: unidentified brown powder	Death 2:53	No
Component of B: unidentified brown pellets	Death 4:01	No
Component of B: "glue?"‡ (*ch'an su*?)§	Death 3:53	No
Herbal remedy mixture obtained from same store using same prescription (C)	No death	No
Different components of C	No death	No
Ch'an su (D)	Death 6:30	1:1 H_2O

*See text for description of samples A through D.

†Prepared by the patient, instructions direct that the herbs boil in 4 bowls of water (approximately 425 ml) until the volume is reduced to 1 bowl (3 to 4 hours). After boiling, a separate package of "glue" is mixed with the tea.

‡"Glue" is "gelatinum asini" powder (ass-hide glue), a granular, powdery resinous material contained in a separate package. It is the same material used to make the gelatinum asini balls. This material is added immediately before drinking and after the other herbs have boiled for several hours.

§*Ch'an su* is a traditional Chinese herb consisting of dehydrated toad gland secretion formed into a resinous block.

But-Lau Method

Step 1	15 ml of the aqueous brewed herbal remedy are adjusted to pH = 9, using 1:1 (vol/vol) concentrated ammonium hydroxide:water
Step 2	Add 20 ml of diethyl ether and sonicate for 5 minutes
Step 3	Save the ether extract in a 125-ml separator funnel Repeat step 2 and pool the second ether extract
Step 4	Add 25 ml of 2% HCl to the separator funnel containing the pooled ether extracts and shake gently for 1 minute
Step 5	Repeat step 4 three times, saving the aqueous phase (total of 100 ml of 2% HCl)
Step 6	Adjust the aqueous phase to pH = 9 with concentrated ammonium hydroxide
Step 7	Extract the aqueous phase with 25 ml of diethyl ether
Step 8	Repeat step 7 three times, saving the combined ether extract in a 250-ml Erlenmeyer flask
Step 9	Dry with 10 grams of sodium sulfate and filter the ether extract
Step 10	Evaporate the ether extract to dryness under a stream of nitrogen using a water bath at room temperature
Step 11	Dissolve the residue in 1 ml of ether

Figure 1.—The But-Lau method of extraction is shown (Paul P. H. But, PhD, and F. W. Lau, Department of Biology and Chinese Medicinal Material Research Center, The Chinese University of Hong Kong, Hong Kong, written communication, June 1993). HCl = hydrochloride

The DHS carried out bioassays and analytical assays on the following specimens:

- The leftover brewed tea (sample A),
- Tea brewed from the second unused portion of the herbal remedy mixture (sample B),
- Tea brewed from a refill of the prescription obtained by DHS from the same store that dispensed the original herbal remedy mixture (sample C), and
- Tea brewed from a control specimen of known *ch'an su* obtained from a local herbalist (sample D).*

A mouse bioassay was done to evaluate the toxicity of these specimens. Three- to 4-week-old Swiss Webster mice of either sex weighing approximately 20 grams were administered intraperitoneally 1 ml of cooled brewed tea of samples A through D prepared as described in Table 1. The mice were kept in a facility accredited by the American Association for Accreditation of Laboratory Animal Care. After the samples were injected, adverse reactions were recorded for about 30 minutes or until death. Surviving mice were reexamined the next morning.

In the analytical assay to identify the specific toxic agents, aqueous leachates of samples A through D were extracted by the But-Lau method (written communication, Figure 1). Analysis was done using both high-resolution mass spectrometry with the direct introduction

*Sample D was obtained and tested after the initial analytical assays identified components of *ch'an su*.

of a probe and gas chromatography with mass spectrometry (Figure 2).

Results

The ingredients in the herbal prescription are listed in Table 2. Based on a literature review, all of the prescribed herbs were nontoxic at the dosages given. According to the Chinese herbalists who examined the unused portion of the herbal remedy, however, one component in the mixture actually dispensed (sample B) did not match the expected prescribed ingredient. The "gelatinum asini" balls were absent, and two unidentified components, small brown pellets and powder, were found that did not resemble any commonly known botanical products. The brown powder was presumably from the breakup of the pellets. The identity of the gelatinum asini powder (ass-hide glue) was questionable.

Postmortem routine toxicologic screening failed to detect either the parent compound or the metabolites of cocaine, amphetamines, opiates, phencyclidine, marijuana, benzodiazepines, ethanol, volatiles, cyanide, strychnine, barbiturates, tricyclic antidepressants, methadone, or other commonly abused drugs. Only lidocaine used in the resuscitation effort was detected in the blood during conventional testing. In retrospect, after the causative agent was identified, testing of the serum using the Abbott TDx assay[6] for digoxin showed a concentration of 6.3 nmol per liter (4.90 ng per ml; toxic, >2.6 nmol per liter [>2 ng per ml]).

Mouse bioassay results verified the herbal remedy mixture as being highly toxic (see Table 1). The administration of decoctions of samples A, B, and D, as well as those prepared from the three components of sample B (unidentified brown powder, unidentified brown pellets, and "glue") caused death in as little as 2½ minutes. Diluting the decoctions before administering resulted in a proportional delay in the time of death. The mice receiving samples A, B, or D exhibited similar symptoms that included piloerection, labored breathing, apparent hypoxia (poor color and bulging eyes), oral discharge, extension and twitching of fore and hind limbs, and in some cases, generalized convulsions followed by death. Decoctions prepared from sample C, although allegedly the same herbal remedy mixture as sample B, were not lethal to mice and produced no obvious adverse effects during the period observed.

Preliminary mass spectral data for components of sample B identified that bufodienolides were the principal toxic components. Based on molecular weights assigned from the ammonia chemical ionization spectra of components of sample B and comparison of the high-resolution spectra of components of sample B with a 120,000-spectra database, including those of the known constituents of *ch'an su*,[7,8] the four major constituents appeared to be bufotalin, cinobufotalin, γ-bufotalin (or its isomer, bufogenin B), and bufalin. Subsequently, samples A through D were extracted under identical conditions, and their total ion current chromatograms from gas chromatography with mass spectrometry are shown in Figure 3. Samples A, B, and D had patterns identical to the major fragments from the bufotalin and bufotenin library mass spectra. None of these compounds were found in sample C.

TABLE 2.—*Prescription for a Chinese Herbal Remedy Provided to the Patient*

Herb	*Quantity, grams*
Astragalus root	15
Gelatinum asini ball (*Equus osinus*)*	18
Cacumen biotae (biota tops, *Bioto orientolis*)	15
Alismatis rhizome	18
Peony root	15
Glycyrrhizoe species root, raw	6
Rehmannia root, cooked	30
Cornus fruit	15
Phellodendron bark (*Phellodendron omurense*)	4.5
Porio species, with host wood attached	24
Gelatinum asini powder†	15

*Gelatinum asini powder (ass-hide glue) plus talcum powder baked for 5 minutes.
†In a separate package, to be added after the volume has been reduced.

Discussion

Ch'an su was identified as the toxic ingredient after mass spectral analysis indicated the presence of known constituents of this ingredient in the specimens. Testing the victim's postmortem serum revealed unexpected, lethal amounts of cardiac glycosides. Based on this information, the expert herbalists' evaluation, the deceased's symptoms, and the results of the bioassay, we concluded that *ch'an su* was the causative toxic agent and had been placed in the herbal remedy mixture instead of the prescribed gelatinum asini (ingredient used to make the gelatinum asini balls and gelatinum asini powder). The final unanswered question was, "How did this substitution occur?" Public health investigation, though limited, did not suggest that a contaminated batch of toxic herbs had been imported into the community. Investigation of the circumstances by the medical examiner's office and the DHS did not uncover any facts to indicate that a deliber-

Gas Chromatography-Mass Spectrometry

Each extract of herbal remedy was injected separately into the Hewlett Packard (HP) 5890 gas chromatograph (GC) with an HP 5971A mass selective detector. The conditions for the GC system are as follows: splitless injections of 2 µl were made into a 15-m, 0.25-µm internal diameter DB-1 column with 0.25-µm film thickness; the initial column temperature was 150°C for 2 minutes, ramped at a rate of 20°C per minute until it reached 300°C and held for 12 minutes; linear velocity of the column was 35 cm per second; the transfer line temperature was 310°C. The mass spectroscopy work was performed in the full-scan mode, with the scan range from 35 to 650 atomic mass units and the scan time 1 scan per second, with a solvent delay of 5 minutes and electron multiplier voltage of 1,976 volts.

Figure 2.—The method of gas chromatography with mass spectrometry is described.

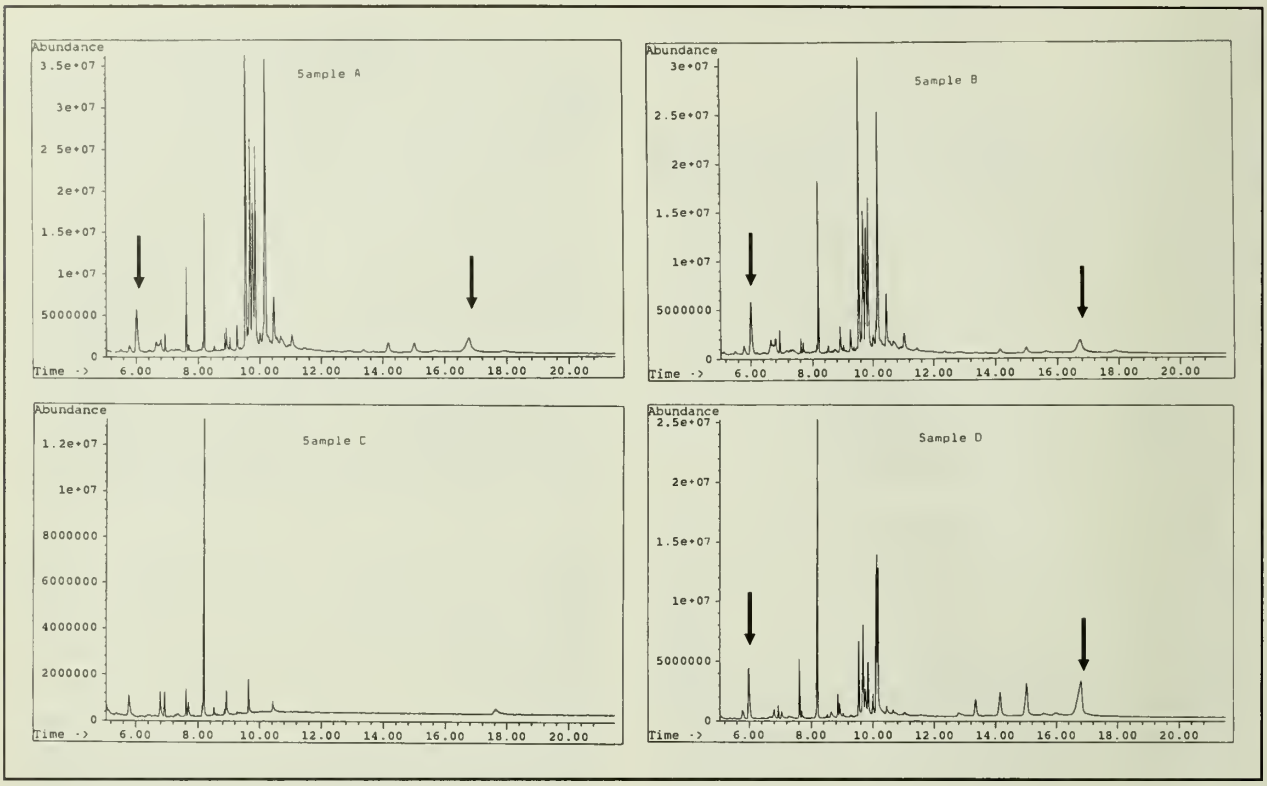

Figure 3.—The four total ion current chromatograms corresponding to samples A, B, C, and D, respectively, are shown. A compound having a retention time of 16.7 minutes has similar mass spectral peaks in samples A, B, and D and the bufotalin library mass spectrum. Samples A, B, and D also contain another compound that has a retention time of 6.0 minutes and major fragments that are identical to the library reference mass spectra of 3-[2-(dimethylamino)ethyl]-1H-indol-5-ol (bufotenin). Sample C has neither of these compounds in the extract.

ate substitution had occurred. Because *ch'an su* and gelatinum asini are both imported as dark-brown resinous blocks that become virtually indistinguishable when ground into powder or pellets, we conclude that the most likely scenario was an inadvertent substitution of *ch'an su* when the herbal prescription was dispensed.

Ch'an su, also known as toad venom, *senso*, or "bufonis venenum," is a concentrated secretion of parotid and sebaceous glands from either *B b gargarizans* Cantor or *B melanosticus* Schneider.[8] These preparations contain two groups of toxic compounds: the steroid derivatives that resemble cardiac glycosides, consisting of bufagenins (bufagins, bufadienolides) and bufotoxins, and the basic components that include epinephrine (adrenaline), norepinephrine, serotonin, and bufotenin (a hallucinogenic compound).[9-11] Traditional uses for *ch'an su* given in minute doses include the stimulation of myocardial contraction, diuresis, pain relief, anti-inflammatory effects, and topical use for skin eruptions. Toad venom has been reported to be abused either by "licking or smoking" to obtain the hallucinogenic effects.[12]

The signs and symptoms of *ch'an su* poisoning may include local irritation with profuse salivation; perioral numbness; nausea; vomiting; pain; arrhythmias such as ventricular fibrillation, tachycardia, bradycardia, and second-degree atrioventricular block; vasoconstriction; hypertension; hallucination; and seizures.[2-4,10,12,13] Many of these symptoms were displayed by the patient during the short clinical course. Although *ch'an su* toxicity in humans has been treated with supportive therapy, there is no known antidote for such poisoning. The use of a pacemaker for severe arrhythmias and charcoal lavage to absorb the toxic components has been suggested.[1,12] In dogs, the administration of propranolol has successfully reversed ventricular fibrillation caused by bufotoxin poisoning.[14]

Structural similarity between the cardiac glycosides of the toad venom and digoxin explains many of the observed symptoms and the cross-reaction in both the digoxin fluorescent immunoassay (Abbott TDx assay) and in radioimmunoassays. Several authors have referred to this finding as the presence of a digoxin-like immunoreactive substance.[2,15,16] In this case, we used the patient's elevated "digoxin" levels to confirm *ch'an su* as the toxic substance. The treatment of severe digoxin and digitoxin overdose with digoxin-specific immune Fab antibodies has been described.[17] Unfortunately, there is no research on the use of digoxin-specific Fab fragments with the cardiac glycosides found in *ch'an su*. Studies of polyclonal digoxin immune Fab with digoxin, digitoxin, and two common digoxin-derived glycosides, however, showed no important difference in the binding

capacities and the ability of the antibodies to abolish the arrhythmogenic effects of these glycosides.[18] This indicates a potential for the use of digoxin-specific Fab fragments in future cases of severe poisoning by *ch'an su* or other naturally occurring glycosides.

This case illustrates several possible problems with the evaluation and use of Chinese herbs. First, the generally accepted definition of a "herbal remedy" needs to be expanded. Chinese herbal remedies may contain not only botanical but also mineral and animal-derived ingredients. Therefore, in evaluating and identifying herbal remedies, consideration must be given to the likelihood of ingredients from a nonbotanical source.

Second, we must remember that many of the most effective pharmaceutical agents used today are based on products initially prescribed as herbal remedies. Many Chinese herbs continue to be commonly prescribed that exhibit potent pharmacologic activities and that may become deadly if not processed, prescribed, dispensed, or used properly.[19,20] Access to these products needs to be limited to professionals who possess the knowledge required to properly identify and use them. Although many western-trained herbalists have a broad-based knowledge of traditional Chinese medicine, dispensers in local herb stores often have not received formal training or apprenticeship and may have insufficient knowledge to dispense such potent pharmacologically active herbal remedies. Both China and Taiwan have laws regulating the use of the most toxic herbs, and proposed regulations on potent herbs used in Chinese medicine are being discussed in Hong Kong.[21] In the United States, not only should herbs be subject to the US standards of approval, but there is a growing need for uniform standards of practice in the herbal industry, to ensure that the herbal products being dispensed are of the highest quality and properly processed and to guard against errors during their dispensing.

Third, the availability and use of Chinese herbs are increasing in the United States and are no longer limited to Asians. A recent study concerning the prevalence of unconventional therapies found that 1% of the general population in the United States has used herbal medicines.[22] Of those who also saw a physician, almost three quarters did not inform the physician of their additional alternative therapies. Even with knowledge of their patients' use of herbal remedies, most traditionally trained US physicians are unfamiliar with herbal properties and toxicities. Physicians and other health care professionals, especially those in geographic regions with ethnically diverse populations, need to become more sensitive to patients' use of alternative therapies. When those therapies involve herbal products, they need to familiarize themselves with their pharmacologic actions, interactions, and toxicities, just as physicians would with any other prescription medication. The use of the digoxin fluorescence immunoassay and digoxin-specific Fab fragments is an example of where knowledge may provide a rough toxicologic screen or suggest possible treatment modalities.

The rapidly growing herbal industry in the United States is substantially less regulated than its western medicine equivalent. Without uniform standards of practice and licensing of herbal practitioners and dispensers, consumers of herbal remedies have no assurance that products they receive are safe. The current public protest against government regulation needs to be examined critically in light of the serious public health ramifications, exemplified by this case, that may occur with the use of unregulated products or unlicensed practitioners.

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REFERENCES

1. Kwan T, Paiusco AD, Kohl L: Digitalis toxicity caused by toad venom. Chest 1992; 102:949-950

2. Lin CS, Lin MC, Chen KS, et al: A digoxin-like immunoreactive substance and atrioventricular block induced by a Chinese medicine 'kyushin.' Jpn Circ J 1989; 53:1077-1080

3. Chern MS, Ray CY, Wu D: Biologic intoxication due to digitalis-like substance after ingestion of cooked toad soup. Am J Cardiol 1991; 67:443-444

4. Hitt M, Ettinger DD: Toad toxicity. N Engl J Med 1986; 314:1517-1518

5. Licht LE: Death following possible ingestion of toad eggs. Toxicon 1967; 5:141-142

6. Cheung K, Hinds JA, Duffy P: Detection of poisoning by plant-origin cardiac glycoside with the Abbott TDx Analyzer. Clin Chem 1989; 35(pt 2):295-297

7. Brown P, Kamano Y, Pettit GR: High-resolution mass spectrometry—Bufadienolides I. Organic Mass Spectrom 1972; 6:47-74

8. Hsu HY, Chen YP, Shen SJ, Hsu CS, Chen CC, Chang HC: Oriental Materia Medica—A Concise Guide, 1st edition. Long Beach, Calif, Oriental Healing Arts Institute, 1986, pp 770-772

9. Meyer K: Cardiotoxic steroids from toads. Memorial Inst Butanian 1966; 33:433-440

10. Bedford PGC: Toad venom toxicity and its clinical occurrence in small animals in the United Kingdom. Vet Rec 1974; 94:613-614

11. Chen KK, Kovaříková A: Pharmacology and toxicology of toad venom. J Pharm Sci 1967; 56:1535-1541

12. Mack RB: Kiss me and the world is mine. N C Med J 1990; 51:375-377

13. Eliades D, Swindall B, Johnston J, Pamnani M, Haddy F: Hemodynamic effects of bufalin in the anesthetized dog. Hypertension 1989; 13(pt 2):690-695

14. Palumbo NE, Perri S, Read G: Experimental induction and treatment of toad poisoning in the dog. J Am Vet Med Assoc 1975; 167:1000-1005

15. Lin CS, Lin MC, Chen KS, Liu CB: Effect of a Chinese medicine 'kyushin' on serum digoxin concentration measurement in dogs. Jpn Circ J 1989; 53:108-112

16. Valdes R: Endogenous digoxin-like immunoreactive factors: Impact on digoxin measurements and potential physiological implications. Clin Chem 1985; 31:1525-1532

17. Smith TW, Butler VP, Haber E, et al: Treatment of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. N Engl J Med 1982; 307:1357-1362

18. Cambridge D, Morgan CR, Allen G: Digoxin and digoxin derivative induced arrhythmias: In vitro binding and in vivo abolition of arrhythmias by digoxin immune Fab (DIGIBAND). Cardiovasc Res 1992; 26:906-911

19. Tai YT, But PPH, Young K, Lau CP: Cardiotoxicity after accidental herb-induced aconite poisoning. Lancet 1992; 340:1254-1256

20. Chan TYK, Chan JCN, Tomlinson B, Critchley JAJH: Chinese herbal medicines revisited: A Hong Kong perspective. Lancet 1993; 342:1532-1534

21. Working Party on Chinese Medicine—Interim Report. Hong Kong, Government Press, 1992

22. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL: Unconventional medicine in the United States—Prevalence, costs, and patterns of use. N Engl J Med 1993; 328:246-252

Radiologic Findings of the Hantavirus Pulmonary Syndrome

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THE PATIENT, a 19-year-old male smoker, was admitted to a rural Utah hospital in August 1994 with a dry cough, body aches, and fever to 39.4°C (103°F). He had been given amoxicillin for pharyngitis by another physician two days before admission. He reported recently cleaning mice feces and nests from an old house. On the initial examination, his respiratory rate was 24 breaths per minute, and pulse oximetry showed 90% saturation with the patient breathing 5 liters of oxygen per minute by nasal cannula. He had no retractions, rales, or wheezes. His heart was unremarkable.

Laboratory studies revealed a leukocyte count of 25.8×10^9 per liter (25,800 per mm^3), a hematocrit of 0.52 (52%), platelet count 24×10^9 per liter (24,000 per mm^3), and a lactate dehydrogenase level of 741 U per liter. Arterial blood gas measurements with the patient breathing room air revealed a pH of 7.52, a P_{CO_2} of 23 mm of mercury, and a P_{O_2} of 45 mm of mercury. The serum bicarbonate level was 19 mEq per liter. Chest radiographs (Figure 1) showed bilateral alveolar and interstitial infiltrates.

Within two hours of admission, the patient's respiratory rate increased to 28 breaths per minute. He felt intense breathlessness, and suprasternal retractions developed. The patient was transferred to another hospital with intensive care facilities where supportive care was continued. He did not require intubation.

The diagnosis of hantavirus pulmonary syndrome was suspected and later proved by the elevation of both immunoglobulin (Ig) M and IgG levels.

Discussion

The differential diagnosis suggested by this patient's chest x-ray findings is broad, including viral pneumonia, *Mycoplasma* species pneumonia, psittacosis, *Pneumocystis carinii* pneumonia, toxic inhalation, allergic alveolitis, transfusion reaction, and heroin abuse.

In this patient, however, the history of exposure to mice feces raises the question of the hantavirus pulmonary syndrome. The radiographic findings of hantavirus pulmonary syndrome have recently been described[1] and, as with this patient, often show interstitial and alveolar infiltrates. The patient's history, the rapid deterioration of his condition, elevated hematocrit, elevated lactate dehydrogenase level, and low platelet count support the diagnosis of the hantavirus pulmonary syndrome.

Recent reviews of the hantavirus pulmonary syndrome suggest that fever and myalgia are the most common symptoms and that tachypnea is the most common sign.[2-4] The laboratory diagnosis of the syndrome rests on serologic tests to detect IgM to hantavirus or a four-

(Peterson MC, Bastian BV, Tatton JA: Radiologic findings of the hantavirus pulmonary syndrome. West J Med 1996; 164:76-77)

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Figure 1.—**Left,** Posteroanterior and, **right,** lateral chest x-ray films obtained at the time of admission are shown. They reveal poorly defined alveolar nodules that are most prominent in the upper lobes and widespread interstitial linear opacities, with many septal lines seen at the bases.

fold rise in the IgG level, the amplification of viral nucleotides by polymerase chain reaction, or immunohistochemistry to detect antigen to hantavirus. Treatment of the syndrome is mostly supportive; however, an open-label trial of ribavirin has been in progress.

REFERENCES

1. Ketai LH, Williamson MR, Telepak RJ, et al: Hantavirus pulmonary syndrome: Radiographic findings in 16 patients. Radiology 1994; 191:665-668

2. Butler JC, Peters CJ: Hantaviruses and hantavirus pulmonary syndrome. Clin Infect Dis 1994; 19:387-395

3. Duchin JS, Koster FT, Peters CJ, et al and the Hantavirus Study Group: Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994; 330:949-955

4. Hjelle B, Jenison S, Mertz G, Koster F, Foucar K: Emergence of hantaviral disease in the southwestern United States. West J Med 1994; 161:467-473

Human Orf in Los Angeles County

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ORF, also known as ecthyma contagiosum, "farmyard pox," and ovine pustular dermatitis, is a proliferative cutaneous viral disease transmitted to humans by contact with infected sheep, goats, and occasionally wild ungulates (hoofed animals).[1,2] The causative agent is a DNA virus belonging to the genus *Parapoxvirus* and family Poxviridae. It is endemic in northern California and in rural areas worldwide.[3] Human lesions can be solitary or multiple and are usually located on hands, arm, or face. After an incubation period of three to ten days, a macular or papular lesion appears that progresses to a nodule, with subsequent verrucous changes and crusting in four to six weeks.

We report a case of orf in a woman after traumatic contact with a lamb's head. According to the Los Angeles County Department of Health Services medical epidemiologist, this is the first case of orf reported in Los Angeles County, California.

Report of a Case

The patient, a 52-year-old woman, was preparing a lamb for a family banquet when she accidentally scratched her right wrist on a lamb's tooth. She initially cleaned the wound with alcohol and iodine. Two days later, she noted a small red swelling over the site of injury that then progressed to a vesiculonodular lesion in a week's time. She presented to an emergency department in April 1994, and a 1-cm erythematous, nontender papule with mild fluctuance was noted over the anterior surface of the right wrist. She had full range of motion of her wrist and had reported no fever, chills, night sweats, myalgia, colds, cough, swollen glands, or arm swelling. Incision and drainage revealed bloody discharge, and she was sent home with a regimen of dicloxacillin sodium, 500 mg four times a day for five days. On a follow-up visit a week later, her lesion was firm, slightly tender, red, and had enlarged to about 1.5 cm. Her wound was cleaned with povidone-iodine solution, and the use of ibuprofen, 600 mg three times a day, was prescribed. She was then referred to the infectious diseases clinic for an opinion.

On physical examination, the patient appeared well and was afebrile. She had a 1-cm yellow and brown crusted, nontender nodule over the volar surface of the right wrist; no ulnar or axillary lymphadenopathy was present.

Because of her clinical presentation and exposure to the lamb's head, the diagnosis of orf was considered. She was then referred to the dermatology service where a shave biopsy of the skin lesion (Figure 1) was done. On subsequent follow-up, the lesion did not recur, and there was only minimal scar formation over the biopsy site.

Discussion

To our knowledge, this is the first case of orf reported to the Los Angeles County Health Department. Increased awareness among sheepherders of the presence of orf in sheep ("scabby mouth") and the decreasing population of sheep and goats in the county may account for the rarity of cases (D. E. Dassey, MD, Los Angeles County Department of Health Services, written communication, July 1994).

The name "orf" is an Anglo-Saxon designation for cattle and is actually a misnomer because this disease is seen only in sheep, goats, and camels, and not in cattle.[4] The etiologic agent for this disease is a dermatotropic poxvirus. It is transmitted from infected dead or alive animals, especially through infected saliva. Fomites may

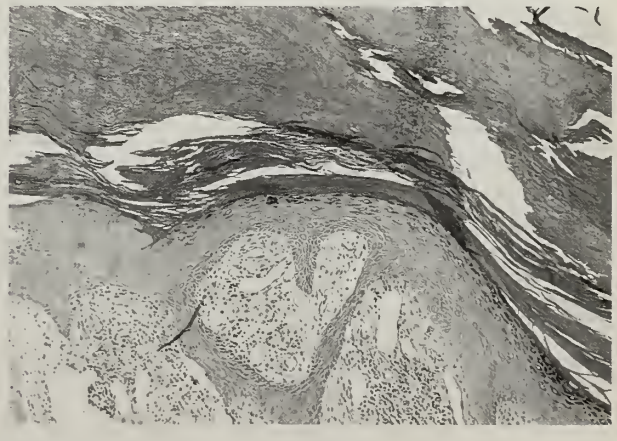

Figure 1.—A skin biopsy shows crusting acanthosis, papillomatosis, and pronounced chronic inflammation, consistent with the regenerative phase of orf.

(Lo C, Mathisen G: Human orf in Los Angeles County. West J Med 1996; 164:77-78)

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also be a source of transmission because viral infectivity may be present for several years.[4,5] The diagnosis of orf should be suspected when there is a characteristic lesion and a history of direct or indirect contact with sheep.

Six stages of the disease have been described, both in sheep and in humans.[5] There is an initial maculopapular stage (1 to 7 days), in which the lesion appears as an erythematous elevated spot. This is followed by a "target" stage (7 to 14 days) when the lesion is characterized by a red center surrounded by a white ring and a red halo. Lesions then become nodular in the acute stage (14 to 21 days), begin drying and crusting in the regenerative stage (21 to 28 days), progress to small papillomas (28 to 35 days), and eventually to a regressive stage (35 days to cure) when they crust and heal. The differential diagnosis of this skin lesion includes infectious and noninfectious diseases such as cutaneous anthrax, staphylococcal skin infection, mycotic skin infections, such as coccidioidomycosis or sporotrichosis, atypical mycobacterial infections, nocardiosis, tularemia, giant molluscum contagiosum, milker's nodule (paravaccinia), pyogenic granuloma, keratoacanthoma, and skin cancer.

The histopathologic study of lesions is the current readily available tool for diagnosis. Early lesions (stage 1 and 2) show vacuolated keratinocytes with intranuclear and intracytoplasmic inclusions, focal epidermal necrosis, and dermal inflammation. As the lesion progresses to resolution, there is regeneration of the epidermis with papillomatous fingerlike projections of the epidermis into the dermis and collagen formation.[4,5]

The definitive diagnosis of orf is obtained by electronmicroscopic visualization of the characteristic virus in the cytoplasm of keratinocytes or isolating the virus by culturing a biopsy specimen on lamb fibroblasts. (Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral and Rickettsial Disease Laboratory, oral communication, 1994). Adjunctive diagnostic testing includes serologic titers of orf virus antibodies by complement fixation and the immunofluorescent detection of viral antigen.[4,6,7] Complications are rare and may include fever, rigors, drenching sweats, malaise, urticaria, lymphadenopathy, lymphangitis, a generalized varicelliform eruption of skin and mucous membranes, or erythema multiforme.[4,8,9]

Orf may not need to be treated because it is a self-limited illness. Various treatments have been used, however, to accelerate the healing of lesions. These have included painting lesions with idoxuridine 40% solution in dimethyl sulfoxide and surgical excision.[10,11] Surgical excision may be the treatment of choice because this provides early diagnosis, avoids the complication of secondary bacterial infection and dissemination of lesions, and prevents the development of erythema multiforme.[9,11] Orf should be considered in anyone with a characteristic skin lesion and a history of exposure to sheep or related animal products.

REFERENCES

1. Benenson AS (Ed): Control of Communicable Diseases in Man, 15th edition. Washington, DC, American Public Health Assoc, 1990, pp 311-313

2. Muron T, Biron F, Peyramond D: Orf (Photo Quiz). Clin Infect Dis 1994; 19:349

3. Rucker RC: Clinical picture of orf in Northern California. Cutis 1977; 20:109-111

4. Huerter CJ, Alvarez L, Stinson R: Orf: Case report and literature review. Cleve Clin J Med 1991; 58:531-534

5. Leavell UW Jr, McNamara MJ, Muelling R, Talbert WM, Rucker RC, Dalton AJ: Orf—Report of 19 human cases with clinical and pathological observations. JAMA 1968; 204:109-116

6. Kluge JP, Cheville NF, Peery TM: Ultrastructural studies of contagious ecthyma in sheep. Am J Vet Res 1972; 33:1191-1200

7. Westphal HO: Human to human transmission of orf. Cutis 1973; 11:202-205

8. Lober CW, Mendelsohn HE, Datnow B, Fenske NA: Clinical and histologic features of orf. Cutis 1983; 32:146-147

9. Agger WA, Webster SB: Human orf infection complicated by erythema multiforme. Cutis 1983; 31:334-338

10. Hunskaar S: A case of ecthyma contagiosum (human orf) treated with idoxuridine (Letter). Dermatologica 1984; 168:207

11. Shelley WB, Shelley ED: Surgical treatment of farmyard pox. Cutis 1983; 31:191-192

Commentary

Community-Acquired Pneumonia
Is It Time for the Penicillin Bullet to Be Replaced?

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A common diagnostic and therapeutic problem in medicine is that of community-acquired pneumonia. Penicillin has often been touted as the drug of choice because *Streptococcus pneumoniae* has been considered to be the major cause of community-acquired pneumonia. This concept is intrinsically unsound because communities vary greatly, as do causes of the pneumonia acquired in these communities. Pandemics due to influenza or to other microbes that have been recognized in the past ten years also shift the etiologic profile greatly. Amid these complexities, physicians operate under increasing pressure by managed health systems to provide economical care.

The diagnosis and treatment of pneumonia now require a complicated set of decisions, some of them tainted by litigious pressures. With the current constraints on time and resource use, physicians need to diagnose the cause of community-acquired pneumonia with a minimal number of laboratory studies and to decide if the use of a particular antibiotic for therapy is warranted. Under a system of capitation, physicians must be particularly conservative in the types of laboratory studies and consultants that they use in managing this disorder. Many antibiotics cover most of the major causes of community-acquired pneumonia. It is, therefore, more expeditious to use them de novo rather than to wait for diagnostic studies, including the time-honored sputum Gram's stain and cultures. As the Finnish architect Mies van der Rohe (noted for his architecture characterized by simplicity) said many years ago, "Less is more." To extend this philosophy even further to the economic issues of the 1990s, "Do less and get more." Frequently, in the evaluation of a case of possible community-acquired pneumonia, a chest roentgenogram is obtained. More diagnostic tests may be used if the patient is immunocompromised, does not respond to an antibiotic, or has serious associated illnesses.

Unfortunately, community-acquired pneumonia may now be caused by several newly recognized agents that do not respond well to penicillin therapy. Pathogenic agents such as *Haemophilus influenzae* and *Moraxella catarrhalis* may produce penicillinase that inactivates penicillin. In some communities, 30% to 40% of cases of infection due to *H influenzae* are resistant to penicillin and ampicillin; for infections due to *M catarrhalis*, the prevalence of resistance may be 95% or more. Other agents resistant to penicillin can mimic bacterial pneumonia acquired in the community, for example, *Chlamydia pneumoniae* in elderly patients or *Mycoplasma pneumoniae* in young adults.[1] Therefore, more second- and third-generation cephalosporins (such as cefixime, cefuroxime, or expanded cephalosporins such as cefpodoxime proxetil and loracarbef), generic tetracycline or doxycycline, and the erythromycins (particularly the newer conjugers of clarithromycin and azithromycin) are being used to treat community-acquired pneumonia.

The American Thoracic Society now recommends a "machine-gun" approach to the treatment of pneumonia with a limited use of laboratory tests because of the uncertainties in origin.[2] Stress is given to determining the cause based on the history and physical examination (how Oslerian!). Until a patient's laboratory data indicate a clear cause, treatment is commonly initiated with either a tetracycline (doxycycline), erythromycin (modern alternatives, azithromycin and clarithromycin), or even a quinolone (ofloxacin or ciprofloxacin) in non-immunologically compromised patients. When a patient is immunologically compromised, a cephalosporin is added to one of these three classes of antibiotics. The use of these newer agents is convenient because they are taken once or twice a day for mild to moderate cases of pneumonia. Bacteremia does sometimes occur while pneumonia is being treated with some of these newer antibiotics, but breakthrough bacteremia occasionally occurred even in the early days of the treatment of pneumococcal pneumonia with penicillin.

A decision to use penicillin as a first-line antibiotic for community-acquired pneumonia is further eroded by the emergence of both relative and major resistance to this antibiotic by *S pneumoniae*. Alternative antibiotics in this setting include ceftriaxone sodium and vancomycin. In fact, in some parts of the southern United States, a relative resistance of *S pneumoniae* to penicillin

(Silva J Jr: Community-acquired pneumonia—Is it time for the penicillin bullet to be replaced? West J Med 1996; 164:79-80)

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is found in greater than 50% of patients.[3] This resistance is an increasingly strong argument for immunizing whole segments of our population with a pneumococcal vaccine. The currently available vaccine for *S pneumoniae* incorporates serogroups that include some 80% to 85% of organisms that are found to be the cause of pneumonia in this country. Other nations compound vaccines differently. Unfortunately, serogroup 6A, a common cause now of penicillin resistance, has not been incorporated in current vaccines, but new vaccines are being reformulated.

For community-acquired pneumonia, penicillin can no longer be considered a highly effective first line of defense to be blindly administered for an unknown microbial target.

REFERENCES

1. Bartlett JG, Mundy LM: Current concepts: Community-acquired pneumonia. N Engl J Med 1995; 333:1618-1624

2. Niederman MS, Bass JB Jr, Campbell GD, et al: Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy—American Thoracic Society: Medical Section of the American Lung Association. Am Rev Respir Dis 1993; 148:1418-1426

3. Hofmann J, Cetron MS, Farley MM, et al: The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; 333:481-486

Radiologic Case

Fever, Leukocytosis, and Referred Thigh Pain

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A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

The patient, a 43-year-old man with insulin-dependent diabetes mellitus, presented four days after sustaining a dog bite on his right hand, complaining of excruciating, intermittent, right thigh pain. He was febrile (temperature, 38.3°C [101°F]) and had a leukocyte count of 27.8 × 10^9 per liter (27,800 per mm^3). On physical examination, he had a 2-cm open wound with minimal purulent drainage on the fourth digit of his right hand. He had some limited range of motion of the right hip and focal muscular tenderness in the medial thigh, but no other infectious or neurologic findings. A radiographic evaluation included chest, lumbar, right femur, and pelvic films and a computed tomographic (CT) scan of the abdomen; all were normal. In addition, a nuclear medicine scan showed no signs of infection. A CT scan and a magnetic resonance image (MRI) of the pelvis were done (Figures 1 and 2).

What is the most likely diagnosis in this patient?

What study could be done to confirm the diagnosis?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A computed tomographic scan of the pelvis, axial section, shows a 3-cm mass between the external iliac artery and vein.

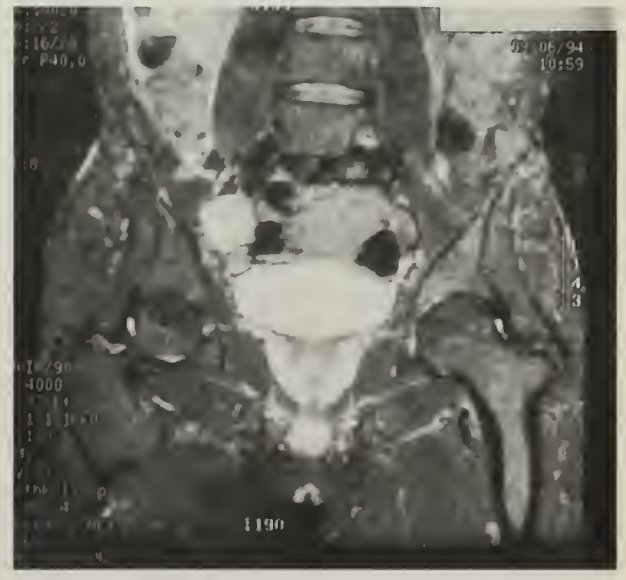

Figure 2.—A magnetic resonance image of the pelvis, coronal section, shows a 3 x 3 x 4-cm mass in the right internal iliac region.

(Dyer KA: Fever, leukocytosis, and referred thigh pain. West J Med 1996; 164:81-82)

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ANSWER: Pelvic schwannoma

THE CT AND MRI SCANS of the pelvis detected a right retroperitoneal mass. A CT-guided fine needle aspirate (FNA) was used to obtain a tissue diagnosis. The biopsy showed a neurilemoma (schwannoma).

Schwannomas are benign nerve sheath tumors of neural crest cells that arise from cranial or spinal nerve roots to form an encapsulated tumor. They make up 10% of intracranial tumors and 25% of intraspinal tumors.[1(pp2171-2173)] These tumors grow slowly and are often asymptomatic. There is no gender preference. They usually occur between the ages of 19 and 69 years.[2] Sensory roots are most frequently affected. The most common intracranial tumor is acoustic neuroma, which attaches to the vestibular branch of the eighth cranial nerve. Presenting symptoms include tinnitus and hearing loss. The sensory portion of the trigeminal nerve (fifth) may also be affected, but less commonly. When extradural, the tumor is generally associated with large nerve trunks and most frequently involves the thoracic region.[1,3(pp1351-1352)] The tumor may originate in the mediastinum or retroperitoneum.[2]

Symptomatic schwannomas can be treated surgically. The tumors are usually well encapsulated and attached to, but easily dissected free from, the nerve. There are reports of recurrences if the tumor has not been completely excised. Rarely do they become malignant.[4,5(pp173-175)]

This case was perplexing because of two concurrent processes, an infection and the thigh pain. Cultures of specimens of blood, urine, and FNA were negative for pathogens. None of the radiographic studies revealed sources of infection. The probable source was the finger wound. The patient responded to empiric treatment with antibiotics with resolution of the fever and elevated leukocyte count. Once diagnosed, the schwannoma was treated by surgical excision, and the leg pain eventually resolved.

Retroperitoneal pelvic tumors are rare: fewer than 24 cases have been reported.[2,6] They frequently present as an asymptomatic mass, and other symptoms include abdominal, leg, or back pain, swelling, uterine bleeding, or occasionally a pathologic fracture.[1,5,7] A pelvic tumor may manifest as referred leg pain. Of the reported cases of retroperitoneal tumors causing leg pain, there was one of lymphoma, one of benign schwannoma, and nine of soft tissue sarcomas. Other reports have shown that pain elicited with the FNA procedure suggests the presence of a neurogenic tumor. This patient had a substantial amount of pain during the biopsy of the mass.[7] Patients may undergo a variety of radiographic studies before the diagnosis of retroperitoneal tumor is made; it is best made with a CT or MRI scan.

REFERENCES

1. Kissane JM (Ed): Anderson's Pathology. 9th edition. St Louis, Mo, CV Mosby, 1990

2. Andrews S, Capen CV: Pelvic schwannoma in pregnancy—A case report. J Reprod Med 1993; 38:826-828

3. Cotran RS, Kumor V, Robbins SL (Eds): Robbins Pathologic Basis of Disease. 5th edition. Philadelphia, Pa, WB Saunders, 1994

4. Ball AB, Serpell JW, Fisher C, Thomas JM: Primary soft tissue tumours of the pelvis causing referred pain in the leg. J Surg Oncol 1991; 47:17-20

5. Sutton D (Ed): A Textbook of Radiology and Imaging. 5th edition. New York, NY, Churchill Livingstone, 1993

6. Gubbay AD, Moschilla G, Gray BN, Thompson I: Retroperitoneal schwannoma: A case series and review. Aust N Z J Surg 1995; 65:197-200

7. Jones HM, Conces DJ Jr, Tarver RD: Painful transthoracic needle biopsy: A sign of neurogenic tumor. J Thorac Imaging 1993; 8:230-232

Editorials

A Rare Twist to a Common Problem

In nature oxalate can have many roles. In some bacteria it is a principal source of energy. In plants, oxalate appears to be important in maintaining calcium homeostasis. Oxalate can be produced in the leaves and bark to precipitate excess calcium as calcium oxalate, which is stored as crystalline deposits within vacuoles of cells, allowing the maintenance of normal calcium balance within the plant. Periodically the leaves and bark are shed, representing a pattern of excretion that allows the plant to be rid of the excess calcium. In humans, oxalate is an end product of metabolism excreted by the kidneys in urine. Herein begins the problem because calcium is abundant in urine. This leads to urine that often is supersaturated with calcium oxalate, with the potential for crystal formation.

Calcium oxalate dihydrate (COD) and calcium oxalate monohydrate (COM), the usual crystalline phases of calcium oxalate, are the predominant crystals in about 70% of stones formed within the urinary tracts of patients from industrialized countries. In the vast majority of patients with calcium oxalate stones, the endogenous production of oxalate is normal and the stone formation that occurs is the product of a multifactorial process in which the concentration of oxalate in the urine is just one of the factors.

In the case described by John J. Kuiper, MD, elsewhere in this issue,[1] a challenging set of problems was present, making it different from the usual clinical setting wherein calcium oxalate stones are formed. In this patient, there were nephrocalcinosis, renal insufficiency, and extrarenal deposits of calcium oxalate (oxalosis), in addition to urinary calculi. All of this suggested the possibility of preazotemic hyperoxaluria. By history and examination, secondary causes of hyperoxaluria were eliminated. What was left was the probability that the patient had one of the forms of primary hyperoxaluria with a metabolic defect that caused endogenous overproduction of oxalate and hyperoxaluria. At age 45, or even 28 when his symptoms began, the patient would be expected to have primary hyperoxaluria type II because the age of onset of symptoms is at least a decade later than is the case with patients with primary hyperoxaluria type I.[2,3] Instead, when the patient's siblings were examined, one was found to have hyperoxaluria and glycolic aciduria, confirming the diagnosis of primary hyperoxaluria type I.

Vigorous dialysis followed by liver and kidney transplantation and treatment with magnesium citrate until the massive body stores of oxalate were mobilized and excreted has relieved the patient's problems and corrected the metabolic defect that caused the endogenous overproduction of oxalate.

When the patient was seen in 1991, "the horse was already out of the barn." He was in renal failure requiring dialysis, and there was already evidence of substantial oxalosis in the bone. At this stage of the disease, dialysis in any form is unable to keep up with the endogenous oxalate production. If nothing else is done, oxalosis with all of its complications progresses to a painful death. Kidney or liver and kidney transplantation are necessary if the patient is to survive and lead a productive life. The presence of oxalosis, particularly when it is advanced, complicates transplantation and reduces the chance of success.[4] Early diagnosis and treatment are vital to the well-planned management of patients with primary hyperoxaluria. Medical management can prevent or prolong the onset of serious complications.[3] Oral treatment with neutral orthophosphate, magnesium, or citrate to decrease supersaturation and increase the inhibition of calcium oxalate crystal formation have all been described.[3-9] Those patients with primary hyperoxaluria type I who respond to the administration of pyridoxine with a reduction in the urinary excretion of oxalate to normal or near normal can be managed with vitamin B_6 supplementation. If a patient is known to respond to vitamin B_6 supplements and presents in renal failure, kidney transplantation alone with long-term vitamin B_6 treatment after transplantation would be the favored approach. If the patient has type II hyperoxaluria, an excellent response can be expected to medical treatment that decreases supersaturation and increases the inhibition for calcium oxalate crystal formation.[3] Because these patients with type II hyperoxaluria do respond well to medical treatment, the rare patient with renal failure should have kidney transplantation followed by long-term medical treatment. The use of pyridoxine is not indicated in patients with type II hyperoxaluria because it will have no effect on the oxalate production and urinary excretion.

Patients with pyridoxine-resistant hyperoxaluria type I will often follow the course of the patient described by Kuiper.[1] The most notable exception is the age of the onset of symptoms. Many of these patients have symptoms by age 5, and many are dead by age 20 if not treated medically.[10] In retrospect, this patient had his first symptoms at age 28 when a urinalysis was obtained and showed "4+ calcium oxalate crystals." This was a vital clue that could have led to the underlying diagnosis. A finding of 4+ calcium oxalate crystals rarely occurs in the urine of patients without hyperoxaluria. Further, it is highly likely that most (if not all) of these crystals were COM, a crystal phase that typically is present in untreated patients with primary hyperoxaluria of either type with substantial hyperoxaluria.[11] On the other hand, COD is the crystal phase that is usually present in the urine of normal subjects and patients with the common forms of calcium oxalate stone formation. To stabilize the COD phase of calcium oxalate in urine, normal inhibitors of calcium oxalate crystal growth need to be present in normal concentrations.[12] Patients with primary hyperoxaluria not receiving treatment often have reduced concentrations of these inhibitors in their urine, probably due to surface absorption of these inhibitors to the many crystals that are present in their

urine.[13] Patients with common causes of calcium oxalate urolithiasis do not have a reduction of these inhibitors. On three more occasions, the same observation was made with urinalysis for this patient and apparently not pursued. If the diagnosis had been made during that time and appropriate medical treatment started, it is possible that the major medical resources that were needed to help the patient survive could have been postponed or avoided.

All too often the diagnosis and treatment in patients with primary hyperoxaluria are delayed until major complications such as renal failure and oxalosis have set in. By then, treatment alternatives are limited. In the past, urinary oxalate was difficult to measure accurately because of the difficulty of measuring it in biologic fluids. With the availability of rapid, simple, and accurate methods to measure oxalate, this is no longer a problem. Good oxalate measurements are available from many sources and should be used when patients have recurrent calcium oxalate stones. Any patient younger than 20 years with calcium oxalate urolithiasis should have their urinary oxalate excretion measured. If hyperoxaluria is detected, the cause should be determined. Secondary causes should be sought, and if none are present, then evaluation should be done for one of the types of primary hyperoxaluria. Kuiper has provided us with an extremely useful list of sources to help with this evaluation. In addition to oxalate, urinary glycolate and L-glycerate excretion should be measured because confirming the type will help in planning the treatment strategy. Consultation with a specialist experienced in the management of patients with primary hyperoxaluria may be extremely helpful in the early stages of the workup and treatment planning.

In summary, the following three points can be made from this unusual case:

- Include the measurement of urinary oxalate in the laboratory workup when indicated.
- Early diagnosis while renal function is intact is critical in the long-term care of patients with primary hyperoxaluria.
- Effective medical treatment is available to prevent the complications of primary hyperoxaluria in many of these patients.

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REFERENCES

1. Kuiper JJ: Initial manifestation of primary hyperoxaluria type I in adults—Recognition, diagnosis, and management. West J Med 1996; 164:42-53

2. Chlebeck PT, Milliner DS, Smith LH: Long-term prognosis in primary hyperoxaluria type II (L-glyceric aciduria). Am J Kidney Dis 1994; 23:255-259

3. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH: Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med 1994; 331:1553-1558

4. Watts RWE, Morgan SH, Danpure CJ: Combined hepatic and renal transplantation in primary hyperoxaluria type 1: Clinical report of nine cases. Am J Med 1991; 90:179-188

5. Gibbs DA, Watts RWE: The action of pyridoxine in primary hyperoxaluria. Clin Sci 1970; 38:277-286

6. Watts RWE, Veall N, Purkiss P, Mansell MA, Haywood EF: The effect of pyridoxine on oxalate dynamics in three cases of primary hyperoxaluria (with glycollic [sic] aciduria). Clin Sci 1985; 69:87-90

7. Frederick EW, Rabkin MT, Richie RH Jr, Smith LH Jr: Studies on primary hyperoxaluria—I. In vivo demonstration of a defect in glyoxylate metabolism. N Engl J Med 1963; 269:821-829

8. Dent CE, Stamp TC: Treatment of primary hyperoxaluria. Arch Dis Child 1970; 45:735-745

9. Leumann E, Hoppe B, Neuhaus T: Management of primary hyperoxaluria: Efficacy of oral citrate administration. Pediatr Nephrol 1993; 7:207-211

10. Hockaday TDR, Clayton JE, Frederick EW, Smith LH Jr: Primary hyperoxaluria. Medicine (Baltimore) 1964; 43:315-345

11. Werness PG, Bergert JH, Smith LH: Crystalluria. J Crystal Growth 1981; 53:166-181

12. Martin X, Smith LH, Werness PG: Calcium oxalate dihydrate formation in urine. Kidney Int 1984; 25:948-952

13. Smith LH: Hyperoxaluric states. *In* Coe FL, Favus MJ (Eds): Disorders of Bone and Mineral Metabolism. New York, NY, Raven Press, 1992, pp 707-727

Lessons From the Practice

The Right Question

DANA FREDERICK HOCH, MD, *San Jose, California*

Mai, a 52-year-old Vietnamese woman, seemed more upset than usual. She had arrived in the United States just three years ago. Her parents and much of her family had been killed during the war, but a brother had made it to San Jose, California, in the late 1970s. He had sponsored Mai's immigration, and she had moved in with him and his family. Her medical problems included diabetes mellitus, chronic renal failure, painful neuropathy, hypertension, and degenerative arthritis. She had been my patient for two years; most of her visits to the clinic were frustrating for both of us.

For many months I listened attentively as she complained to me through Duc, our Vietnamese interpreter. Many of her symptoms persisted: chronic headaches, insomnia, dizziness, and back pain. I compulsively did workups for her symptoms, but the longer they persisted and the more tests I ordered, the less I uncovered. No matter which antihypertensive or antidepressant drug I prescribed, no matter what therapist or social agency I referred her to, no matter how compassionate I tried to be, it seemed that I accomplished little. There was never a smile or a "thank you," just tight-lipped grimaces.

Today she shook her head and aimed torrents of high-pitched, squeaky Vietnamese at Duc. Some months before, Mai had had her hair cut short, crew-cut style, in an effort to cure the headaches. She wore a black duck-billed hunter's cap with ear protectors over her gray-speckled hair. Her dark little eyes had a pained look. Her stubby hands and fingers clenched and unclenched the corners of the examination table and left sweat stains on the paper covering. I noticed that her fingernails were bitten to the quick.

"Doctor," Duc began after Mai paused a moment, "she says her chest hurts all the time, with her headaches. And she cannot sleep." He told me this in an indifferent tone, accustomed as he was to hearing these complaints over and over in the clinic.

With an unblinking calm that belied my inner frustration, I said, "Mai, I am concerned about these problems. Also, your blood pressure and blood sugar are too high. That's part of why you feel so sick. I tried you on a pill to take at bedtime for sleep and depression. Did it help?"

Duc translated. Mai let out another burst of anguished speech. "She said the medicine you gave her last visit made her dizzy all day, so she stopped all of her pills."

"You know, Mai," I said with rising exasperation, "you've been coming to see me for two years, but not much has changed. Your symptoms are the same, and now you have stopped the medications for blood pressure and diabetes. How can I help you?"

Duc looked at me sideways and knitted his brow skeptically. He spoke briefly to Mai. "She says only please give her medications for dizziness and headaches and sleeping." My spirits sank visibly. "Mai," I said, "you are very unhappy. What in your life have you ever enjoyed doing, even if you cannot do it now?" The standard inquiries hadn't worked with Mai; I wanted at least to get us out of the muddy rut that had become our relationship.

Once again, Duc gave me a sideways glance and asked Mai the question. Suddenly the forlorn, anxious look vanished, and a smile tugged at the corners of her mouth as she replied.

"She used to paint pictures, but her brother did not like the mess in the garage. Her things are now packed up in boxes, and she cannot paint anymore."

"Painting?" I asked with disbelief. "Like with oils and watercolors?"

"That is what she said. Back in Vietnam, she would stand close by the delta or a river and paint the workers in the rice fields or the soldiers or the helicopters that flew by."

I was incredulous. I could scarcely imagine what her life must have been like 30 years before, what spirit and energy it had taken for a young woman to create art while all around her a war destroyed her family and her country. Suddenly she became a complicated and multidimensional person to me, no longer a non–English-speaking patient whose medical and psychological problems defied all my efforts.

"Well Mai, I want you to get out your brushes and paints. One hour each day. Tell your brother those are 'doctor's orders.' No extra pills. Just take the ones I've been giving you. Don't miss even one day."

One month later she was back. She still wore the ill-fitting cap and looked chronically ill. But her nails had grown out, and her short fingers appeared childlike and delicate. I took her blood pressure and exhaled a sigh of relief. And the finger-stick glucose wasn't normal, but at least it wasn't 400 mg per dl.

Mai spoke quietly to Duc, who then turned to me and said, this time with a conspiratorial smile, "She says 'thank you,' she is much better."

(Hoch DF: The right question. West J Med 1996; 164:85-86)

From the Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, San Jose, CA 95128.
Reprint requests to Dana F. Hoch, MD, Chaboya Clinic, 2410 Senter Rd, San Jose, CA 95111.

"Well, even though you are on the same pills, your sugar and blood pressure are much improved," I said.

"Mai told me that if her legs or head hurt too badly, she rests and takes a pain pill, then it is better."

Mai pulled a painting from a grocery bag and handed it to me. She spoke to Duc with embarrassed smiles and chuckles.

"She wants you to have this picture, Doctor. She painted it after she saw you last. It is from a photograph she kept from Vietnam, one taken near where she grew up."

I held the 24-in by 12-in watercolor at arm's length. It was a jungle scene, a small lake surrounded by palm trees and brush. Mai had used deep blues, greens, and silver to capture the water, its surface pleated by a breeze; palm fronds seemed to toss back and forth on the trees that rimmed the lake; a thatched hut, partially hidden and shaded by bushes, occupied a corner of the background. The striking feature of the painting, however, was two egrets in the foreground. They stood at the water's edge, along a sandy bank. One was busily nosing the shallow water and sand, kicking up droplets and spray. The other one, neck arched gracefully, gazed at its partner; it wore the brightly colored ornamental plumes of the mating season. Taken together, the birds evoked the spirit of hope and the potential of love.

"I am very grateful," I responded awkwardly, moved almost beyond words. "I will keep this special gift at home, in my office." Duc translated. After I handed her her prescriptions, Mai left.

Quite by accident I had asked the right question. On the surface, it had no medical relevance, yet it had been the key to managing this patient's blood pressure and diabetes. The fact that she had been able to share a secret part of her life with me inspired her to finally comply with my treatment. And almost by magic, she and I had discovered how to manage her anxiety and somatic symptoms. Mai did much more than give me a painting; in the process, she had drawn a self-portrait, a portrait of a woman I'd been acquainted with for two years, but had never really known.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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ABSTRACTS JANUARY 1996

(DePalma RG: New developments in the diagnosis and treatment of impotence. West J Med 1996; 164:54-61)

New developments in the diagnosis and treatment of impotence or erectile dysfunction are increasingly based on better understanding of the erectile process. In 1978 it was thought that the failure of arterial inflow was the main cause of male erectile dysfunction. Emphasis was placed on methods of corpus cavernosal revascularization. In recent years, interest has shifted to abnormal cavernosal smooth muscle function. An understanding of the erectile process was greatly enhanced by intracavernosal administration of vasoactive agents in 1982 and, more recently, the use of prostaglandin E_1. These agents promote erection by causing smooth muscle to relax. The intracavernosal administration of vasoactive agents is now used in diagnosis and in therapy. Standard approaches to diagnosis and therapy still vary, but more rational steps are evolving. Considerable progress has been made in quantifying penile blood flow. Increasingly effective therapies are available for an estimated 10 million American men suffering from erectile dysfunction. Therapies include the use of drugs, administering vasoactive agents intracavernosally, vacuum constrictor devices, and vascular interventions in highly selected cases of arterial or venous disease. These procedures are being carefully reevaluated. Critical analysis of recent results suggests that about 7% of men are amenable to vascular interventions, with success rates approximating 70% when supplemental therapy is used.

VASOACTIVE AGENTS IMPOTENCE
ERECTILE DYSFUNCTION

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Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1996, Sun Valley Inn, Sun Valley, Idaho.

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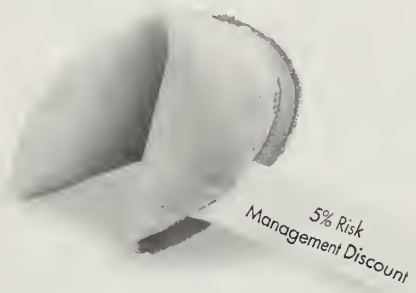

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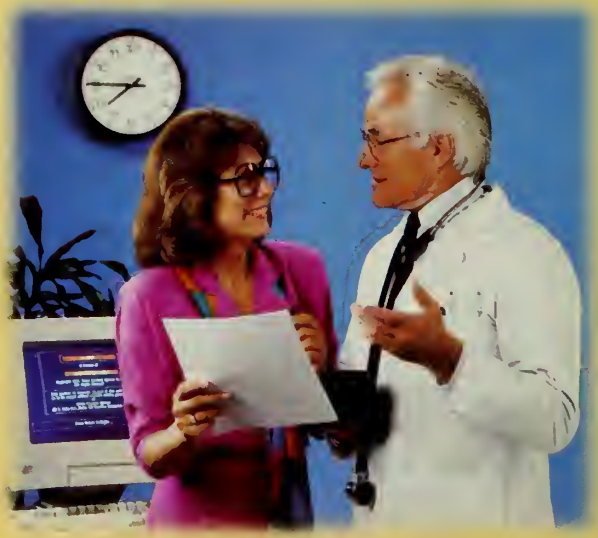

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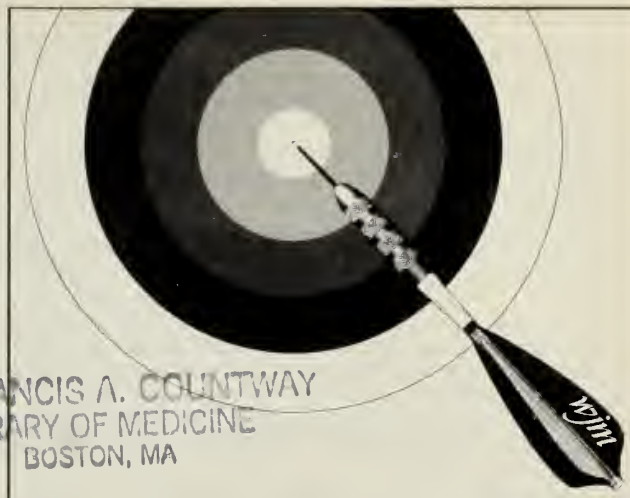

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ABSTRACTS FEBRUARY 1996

(Phinney SD, Siepler J, Bach HT: Is there a role for parenteral feeding in clinical medicine? West J Med 1996; 164:130-136)

Protein-calorie malnutrition as evidenced by loss of weight or of lean body mass is a commonly seen disorder. Although its cause is clearly multifactorial, objective measures of protein-calorie malnutrition have been repeatedly correlated with poor patient outcomes. Total parenteral nutrition was developed to halt or reverse this disorder, but its ability to improve the short- to intermediate-term outcome in patients with impaired nutrient intake has been highly inconsistent. Factors influencing this variable outcome include the degree of functional impairment in the treatment group, the underlying disease causing the impaired intake, and possibly the amount and composition of nonprotein calories delivered. In particular, considerable evidence points to intravenous soybean oil emulsion as a negative factor in the nutritional support of stressed patients. Taken in combination, current information suggests reserving the use of parenteral feeding for patients meeting objective criteria for protein-calorie malnutrition and making parsimonious use of lipid emulsion, especially in stressed patients.

PROTEIN-CALORIE MALNUTRITION **PARENTERAL FEEDING**

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PROTEIN-CALORIE MALNUTRITION **PARENTERAL FEEDING**

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

March 2—**Women and Hypertension.** Arizona Heart Institute at the Ritz-Carlton, Phoenix. Sat. Contact: Cindy Urbaytis. (602) 266-2200x4403.

March 3-6—**10th Annual Magnetic Resonance Imaging Conference.** St Joseph's Hospital and Medical Center and Barrow Neurological Center at the Phoenician Resort, Scottsdale. Sun-Wed. Contact: (602) 406-3067.

March 4-6—**Family Practice Topics.** Interstate Postgraduate Medical Association at the Scottsdale Hilton, Scottsdale. Mon-Wed. Contact: (608) 257-1401.

March 7-9—**Midwinter Symposium: Advances in OB/GYN.** Phoenix OB/GYN Society at the Radisson Resort, Scottsdale. Thurs-Sat. Contact: (602) 267-5366.

March 7-9—**23rd Annual Symposium: Recent Advances in Neurology and Neurosurgery.** University of Arizona College of Medicine with Barrow Neurological Institute at the Phoenician Resort, Scottsdale. Thurs-Sat. Contact: (602) 406-3067.

March 7-10—**19th Annual Mid-Winter Symposium: Advances in Obstetrics and Gynecology**. Maricopa Medical Center and Phoenix OB/GYN at the Radisson Resort Hotel, Scottsdale. Thurs-Sun. Contact: Cathy Clifton, (602) 267-5366.

March 8-9—**Clinical Management of Asthma and Allergic Diseases.** Medical Education Resources at the Hyatt Regency, Scottsdale. Fri-Sat. Contact: (800) 421-3756.

March 10-14—**Radiology in the Desert: Practical Aspects of Radiology and Imaging.** University of Michigan Medical School at the Marriott's Camelback Inn, Scottsdale. Sun-Thurs. Contact: Vivian Woods, (313) 763-1400.

March 14-17—**McDonald Urological Seminar.** Phoenix Urological Society at the Radisson Resort, Scottsdale. Thurs-Sun. Contact: (602) 267-5366.

March 15-17—**Fifth Annual Southwestern Conference on Medicine.** University of Arizona College of Medicine at the Westward Look Resort, Tucson. Fri-Sun. Contact: U of A.

March 18-22—**19th Annual Course: Computerized Tomography of the Body With MRI Correlation.** Society of Computed Body Tomography and Magnetic Resonance at the Scottsdale Princess Resort, Scottsdale. Mon-Fri. Contact: (507) 288-5620.

March 21-23—**Ophthalmic Reviews 1996: Oculoplastics from Coast to Coast.** Mayo Clinic-Scottsdale at the Radisson Resort, Scottsdale. Thurs-Sat. Contact Trish Ghan, Mayo Clinic-Scottsdale.

March 21-24—**1996 Annual Meeting.** Arizona Academy of Family Physicians at the Wyndham Paradise Valley Resort, Scottsdale. Thurs-Sun. Contact: (800) 933-2237.

March 25-27—**Management of the Difficult Airway: Hands-on Workshop and Medical-Legal Issues.** University of Michigan Medical School at the Red Lion's La Posada Resort, Scottsdale. Mon-Wed. Contact: (313) 763-1400.

March 28-30—**Fifth Annual Urogynecology and Disorders of the Female Pelvic Floor.** Mayo Clinic-Scottsdale at The Pointe Hilton Resort at Tapatio Cliffs, Phoenix. Thurs-Sat. Contact: Tamara Zelinski, Mayo Clinic-Scottsdale.

March 30—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale. Sat. Contact: Tamara Zelinsky, Mayo Clinic-Scottsdale.

April 1-3—**Management Strategies in Complex Congenital Heart Disease.** Mayo Foundation at the Point Squaw Peak, Phoenix. Mon-Wed. Contact: (800) 323-2688.

April 9-13—**New Frontiers in Pain.** Maricopa Medical Center at the Radisson Resort Hotel, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

April 10-13—**21st Annual Primary Care Update.** University of Arizona College of Medicine at the Tucson Hilton East, Tucson. Wed-Sat. Contact: U of A.

April 18-20—**Upper Extremity Trauma and Reconstructive Surgery.** Mayo Foundation at The Pointe Hilton Resort, Phoenix. Thurs-Sat. Contact: (800) 323-2688.

April 22-25—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920.

April 28-May 1—**Annual Meeting.** Southwest Surgical Congress at the Marriott's Camelback Inn Resort and Golf Club, Scottsdale. Sun-Wed. Contact: (312) 527-6667.

May 4—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale, Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact Trish Ghan, Mayo Clinic-Scottsdale.

May 6-10—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

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ANESTHESIOLOGY

March 23-28—**24th John J. Bonica Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki, Oahu and Grand Wailea Resort, Maui, Hawaii. Sat-Thurs. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

March 26-29—**5th John J. Bonica Hawaii Pain Conference**. Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (614) 293-8487.

CARDIOLOGY

March 2-9—**Update: Controversies in Cardiovascular Disease.** UCSD at Stouffer Wailea Resort, Maui, Hawaii. Sat-Sat. 21 hrs. $460. Contact: UCSD.

April 13-14—**Practical Advances in Vascular Disease.** Medical Education Collaborative at Loews Coronado Bay Resort, San Diego. Sat-Sun. 10 hrs. $125. Contact: Medical Education Collaborative, 137 W Jewell Ave, Ste 251, Lakewood, CO 80228. (800) 442-6632.

April 25-27—**Sixth Annual Symposium on Coronary Stenting.** Scripps Clinic & Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

March 3-8—**16th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, Medical Conferences, Inc, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 18-22—**Emergency Medicine Symposium II**. UCSD and BSB at La Jolla. Mon-Fri. 32 hrs. $495. Contact: UCSD.

March 27-29—**12th Annual Advances in Emergency Medicine.** USC at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17 hrs. $495. Contact: USC.

May 14-15—**7th Annual High Risk Emergency Medicine**. American College of Emergency Physicians at Hyatt at Fisherman's Wharf, San Francisco. Tues-Wed. 15 hrs. $299 to $499. Contact: Alpen Meeting Service. (800) 451-RISK.

May 31-June 6—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. 18 hrs. $250. Contact: USC.

ENDOCRINOLOGY/METABOLISM

March 13-14—**Advances in Endocrinology and Metabolism.** UCSF at Ana Hotel, San Francisco. Wed-Thurs. 14.5 hrs. $320. Contact: UCSF.

March 15-16—**Diabetes Update.** USC at Ana Hotel, San Francisco. Fri-Sat. 10.5 hrs. $255. Contact: USC.

June 7-11—**Molecular Steriodogenesis**. UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

EPIDEMIOLOGY/INFECTIOUS DISEASE

May 1-3—**17th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17.5 hrs. $410. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

March 1-2—**Pediatric Dermatology for the Primary Care Physician**. UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sat. Contact: UCSF.

March 20-22—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 15 hrs. $325. Contact: UCSF.

March 21-22—**Management of Occupational Health Problems in Primary Care Settings.** Long Beach Regional Medical Education Center at SF/Oakland Bay Bridge Holiday Inn, Emeryville. Thurs-Fri. 15.5 hrs. Contact: COEH-Continuing Education. (510) 231-5645.

April 1-4—**Primary Care in Paradise: Maui 1996**. Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 6-13—**Sixth Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kauai Marriott Resort, Kauai, Hawaii. 29 hours. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez, CA 94553. (510) 372-1457.

April 7-12—**Ninth Annual Primary Care Medicine: Update 1996** UCSF at Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

April 13—**The Team Approach to Oncology: The Primary Care Physician's Role.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 6.5 hrs. $95. Contact: UC Davis.

April 18-21—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hilton Beach and Tennis Resort, San Diego. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 27—**29th Society of Teachers of Family Medicine Annual Spring Conference.** AAFP and Society of Teachers of Family Medicine at the Hyatt Regency at Embarcadero Center, San Francisco. Sat-Wed. Contact: Ray Rosetta, Director of Meetings and Programs, The Society of Teachers of Family Medicine. (800) 274-4512.

May 17-21—**Essentials in Primary Care**. Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

GASTROENTEROLOGY

March 2-3—**Gastroenterology 1996**. The Southern California Society for Gastrointestinal Endoscopy and the Southern California Gastroenterology Society Symposium. SCGSS at Century Park Hotel, San Francisco. Sat-Sun. Contact: Joyce M. Fried, 19327 Pauma Valley Dr, Northridge, CA 91326. FAX (310) 312-9279.

INTERNAL MEDICINE

March 9-16—**Diagnostic and Therapeutic Skills in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kameula, Hawaii. Mon-Fri. 28 hrs. $595. Contact: USC.

March 15-21— **Internal Medicine 1996.** Continuing Medical Education Associates at the Hotel del Coronado, San Diego. Fri-Thurs. 54 hrs. $695. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego, 92138. (619) 223-2997.

April 11-13—**Recent Advances in Hematopoietic Stem Cell Transplantation**. UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. Contact: UCSD.

April 20—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 6 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

May 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

NEPHROLOGY

Aug. 2-8—**12th Comprehensive Nephrology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Thurs. 50 hrs. $800. Contact: UCLA.

OBSTETRICS/GYNECOLOGY

March 26-29—**Hawaii Neonatal and Infant Respiratory Symposium.** Ohio State University at Grand Wailea Resort, Maui, Hawaii. Tues-Fri. Contact: Arlene Rogers, 410 W 10th Ave, Columbus, OH 43210. (619) 293-8487.

OCCUPATIONAL/ENVIRONMENTAL

March 21-22—**Management of Occupational Health Problems in Primary Care Settings.** Long Beach Regional Medical Education Center at SF/Oakland Bay Bridge Holiday Inn, Emeryville. 15.5 hrs. Contact: COEH-Continuing Education. (510) 231-5645.

ONCOLOGY

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders**. Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii, on Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 13—**The Team Approach to Oncology: The Primary Care Physician's Role.** UC Davis at Cancer Center Auditorium, Sacramento. Sat. 6.5 hrs. $95. Contact: UC Davis.

OPHTHALMOLOGY

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

OTOLARYNGOLOGY

May 23-25—**Vestibular Adaptation.** UCLA at Miramar Sheraton Hotel, Santa Monica. Thurs-Sat. 17 hrs. $400. Contact: UCLA.

June 22-28—**1995-1996 Skull Base Surgical Dissection Course**. House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles, CA 90057.

June 29-July 4—**Second International Skull Base Congress and the Seventh Annual Meeting of the North American Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Floor, Los Angeles 90057.

July 5-7—**Current Concepts in Allergy and Otolaryngology**. Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital. Continuing Medical Education Office. 3020 Children's Way (5021). San Diego 92123. (619) 576-4072.

PATHOLOGY

March 18-20—**Current Issues in Blood Substitute Research and Development**. UCSD at Sheraton Harbor Island, San Diego. Mon-Wed. 20 hrs. $500. Contact: UCSD

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 23-25—**Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

March 1-3—**Current Concepts in Pediatric Medicine.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 15.5 hrs. Contact: CME Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

March 28-30—**Pediatric and Adolescent Sports Medicine.** UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 11 hrs. $350. Contact: UCSD.

April 21-23—**Weaning '96.** USC at Stouffer Renaissance Esmeralda Resort, Palm Springs. Sun-Tues. 10 hrs. $525. Contact: USC.

May 16-18—**29th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 16 hrs. $350. Contact: UCSF.

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians**. UCSD at San Diego Hilton Beach & Tennis Resort. Thurs-Sat. 15 hrs. $350. Contact: UCSD.

PLASTIC SURGERY

March 21-23—**8th Annual Symposium on Aesthetic Surgery of the Face.** UCSF. Thurs-Sat. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

April 19-21—**West Coast Neuropsychology Conference.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. 15.5 hrs. $325. Contact: UCSD.

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS, (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037. (619) 554-8556.

RADIOLOGY

March 10-15—**Neuro- and Musculoskeletal MR**. UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $425-$625. Contact: UCSD.

March 10-15—**Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 28 hrs. $626. Contact: UCSD.

March 10-15—**General Radiology Review Course.** UCLA at Guest Quarters Suite Hotel in Santa Monica. Sun-Fri. 40 hrs. $420. Contact: UCLA.

April 6—**UCSD Spring Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $135. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 7-12—**UCSD Neuro and Musculoskeletal MR Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 7-12—**UCSD 16th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 12-14—**UCSD Breast Imaging & Interventions Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375.

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sat-Thurs. 22.5 hrs. $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925 (770) 641-9773.

August 15-18—**Minimally Invasive Therapy of the Brain.** UCSD at Ritz-Carlton Hotel, Marina del Rey. Thurs-Sun. 20 hrs. $495. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

March 21-23—**Eighth Annual Symposium on Aesthetic Surgery.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 18 hrs. $350-$950. Contact: UCSF.

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 26-29—**13th Annual San Diego Shoulder Orthroscopy Meeting.** Tri City Medical Center at Hyatt Regency, La Jolla. Wed-Sat. 24 hrs. $1,375. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Road, Oceanside, CA 92056 (619) 940-2066.

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD at San Diego. Mon-Sat. 36 hrs. $1,395. Contact: UCSD.

UROLOGY

April 25-28—**5th Annual Spring Clinical Nephrology Meetings.** National Kidney Foundation at Disneyland Hotel, Anaheim. Thurs-Sun. 26 hrs. Contact: National Kidney Foundation, Donna Fingerhut. (800) 622-9010.

GENERAL/MULTIDISCIPLINARY

March 2—**The Neuropharmacology of Sleep Medicine.** Scripps Clinic and Research Foundation at Scripps Clinic, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037. (619) 554-8556.

March 22-23—**Out of the Ashes: Can the Private Sector Save Health Care?** Palo Alto Medical Foundation at Fairmont Hotel, San Francisco. Fri-Sat. 12 hrs. $495. Contact: Nancy Collins, Palo Alto Medical Foundation. (415) 853-2911.

April 27-29—**5th Annual Pain Conference: Primary Care Overview of Pain Management.** UC Davis at Tenaya Lodge at Yosemite, Fish Camp. Sat-Mon. Contact: UC Davis.

May 31-June 2—**38th Annual Scientific Meeting of the American Association for the Study of Headache.** San Diego. Fri-Sun. Contact: AASH, (619) 845-1720.

August 8-11—**38th Annual Postgraduate Refresher Course-Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco, CA 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

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AMERICAN COLLEGE OF 1993 ACE ENDOCRINOLOGY

March 1-8—**Colorado Review of Anesthesia.** University of Colorado Health Sciences Center at Marriott's Vail Mountain Resort. Fri-Fri. Contact: U of Colo.

March 3-8—**16th Annual Keystone ENT Conference.** University of Nebraska Medical Center at Keystone Resort, Keystone. Sun-Fri. Contact: U of Nebraska Center for Continuing Education, (800) 642-1095 or (402) 559-4152.

March 10-13—**International Conference on the Fetus and Newborn XXX: Novel Therapies for Neonatal Respiratory Disorders.** University of Colorado Health Sciences Center at Aspen. Sun-Wed. Contact: U of Colo.

March 17-22—**Reconstructive Surgery of the Hip and Knee.** University of Colorado Health Sciences Center at the Ritz-Carlton Hotel. Aspen. Sun-Fri. Contact: U of Colo.

March 23-28—**Geriatrics Board Review Course.** University of Colorado Health Sciences Center at Denver. Sat-Thurs. Contact: U of Colo.

June 6-8—**National Stroke Meeting: The Clinical Aspects of Stroke Diagnosis and Treatment.** Medical Education Resources at Red Lion Hotel and Conference Center, Colorado Springs. Thurs-Sat. Contact: Jaclynna Williams, (303) 798-9683. FAX (303) 798-5731.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 9-10—**The Changing Face of Pediatrics in the '90s.** W. R. Lovelace II Education Center, Lovelace Medical Center, Albuquerque. Sat-Sun. Contact: Steve Yabek, MD, 715 Dr Martin Luther King Dr NE, Albuquerque, 87102. (505) 848-3700.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe, Santa Fe. Thurs-Sun. Contact: UNM SOM.

July 11-14—**New Choices, New Challenges, Psychopharmacology in the Primary Care Setting.** LaFonda Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque, 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**Podiatric Surgical Seminar.** Hotel Santa Fe, Santa Fe. Wed-Thurs. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque, 87108. (505) 262-3468. FAX (505) 262-3194.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

March 3-8—**Advances in Internal Medicine.** Snowbird Cliff Lodge. Sun-Fri. 20 hrs. $450. Contact: UUSM.

March 3-8—**Update in Clinical Microbiology and Immunology.** Olympia Hotel, Park City. Sun-Fri. 25 hrs. $540. Contact: UUSM.

March 8—**Ophthalmology: Resident/Alumni Day.** Fri. 7 hrs. Contact: UUSM.

March 8-9—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

March 10-15—**18th Annual Winter Psychiatry Conference: New Perspectives in Clinical Practice.** The Menninger Clinic at The Yarrow, Park City. Sun-Fri. 28 hrs. $345. Contact: (800) 288-7377.

March 18-20—**Family Practice Refresher Course.** Salt Lake City Hilton Hotel. Mon-Wed. 27 hrs. Contact:: UUSM.

March 22—**Heart Failure Symposium.** University Park Hotel, Salt Lake City. Fri. 5 hrs. $40. Contact: UUSM.

June 23-24—**Otolaryngology in the Intermountain West.** University Park Hotel, Salt Lake City. Sun-Mon. 5 hrs. $50. Contact: UUSM.

July 13-20—**Update in Clinical Microbiology and Immunology.** Snow King Resort at Jackson Hole, Wyoming. Sat-Sat. 25 hrs. Contact: UUSM.

August—**Advanced Obstetrical Life Support.** University Park Hotel, Salt Lake City. 24 hrs. $450. Contact: UUSM.

August 12-16—**Northwest Neuroradiology and Advanced MR Imaging Course.** Pan Pacific Hotel, Vancouver, British Columbia. Mon-Fri. 42 hrs. $1,250. Contact: UUSM.

September 20—**Ophthalmology: Clinical Faculty Day.** Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

October 7-9—**Preconference Workshop.** Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging.** University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology.** Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

MEDICAL GRAND ROUNDS

March 28-30—**4th International Congress on Alport Syndrome.** University Park Hotel, Salt Lake City. Contact: UUSM.

April—**Advanced Techniques in Laryngeal Surgery.** 40 hrs. Contact: UUSM.

April 27—**Advances in the Management of Pain in the Acute and Chronic Settings.** University Park Hotel, Salt Lake City. 6 hrs. Contact: UUSM.

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 7—**Evidence-based Patient Care: Improving Clinical Outcomes.** Seattle. Thurs. Contact: Providence/Seattle Medical Center. (206) 320-2552.

March 7—**Occupational Health in a Managed Care Environment.** Seattle. Thurs. Contact: NW Center for Occupational Health & Safety (206) 543-1069.

March 14-15—**Internal Medicine Review 1996.** Tacoma. Thurs-Fri. Contact: Pierce County College of Medical Education, (206) 627-7137.

March 21—**Advances in Occupational and Environmental Medicine: Infectious Diseases (TB, HIV, Hepatitis) and Other Topics.** Seattle. Thurs. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

April 1-5—**CME at Maui.** Kapalua, Maui, Hawaii. Mon.-Fri. Contact: Pierce County College of Medical Education. (206) 627-7137.

April 3-5—**Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

April 19—**Sixth Annual Health Education Conference: New Practice Models: Integrating Patient & Health Education in a Clinical Setting.** Seattle. Fri. Contact: Providence/Seattle Medical Center. (206) 320-2552.

April 19-20—**Surgical Update 1996.** Tacoma. Fri-Sat. Contact: Pierce County College of Medical Education. (206) 627-7137.

April 26—**Cardiology for Primary Care.** Tacoma. Fri. Contact: Pierce County College of Medical Education. (206) 627-7137.

May 2—**Pesticide Medicine.** Yakima. Thurs. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

May 16—**Women's Health Care.** Seattle. Thurs. Contact: Providence/Seattle Medical Center. (206) 320-2552.

June—**Advanced Statistical Methods in Epidemiology.** Seattle. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

June 7—**Nuts, Bolts, and Innovation in Gastrointestinal Disease III.** Tacoma. Fri. Contact: Pierce County College of Medical Education. (206) 627-7137.

June 12-14—**4th Annual Pacific Northwest Cardiovascular Symposium.** Seattle. Wed-Fri. Contact: Providence/Seattle Medical Center. (206) 320-2552.

June 20-21—**ACLS.** Tacoma. Thurs-Fri. Contact: Pierce County College of Medical Education. (206) 627-7137.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

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TREE CITY USA

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In Memoriam

California Medical Association

Betts, Irvin H., Jr, Visalia. Died Oct 7, 1995, aged 72. Graduate of University of California San Francisco, School of Medicine, 1950. Dr Betts was a member of the Tulare County Medical Society.

Bollinger, Karl J., San Francisco. Died Sept 15, 1995, aged 70. Graduate of University of Zurich, Switzerland, 1953. Licensed in California in 1957. Dr Bollinger was a member of the San Francisco County Medical Society.

Dickson, John Warner, San Diego. Died Sept 15, 1995, aged 63. Graduate of Baylor College of Medicine, Houston, Texas, 1957. Dr Dickson was a member of the San Diego County Medical Society.

Dudley, Donald J., Apple Valley. Died Nov 15, 1995, aged 70. Graduate of Stanford University School of Medicine, California, 1948. Dr Dudley was a member of the San Bernadino County Medical Society.

Fay, Kevin, Santa Barbara. Died Oct 5, 1995, aged 78. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada, 1943. Licensed in California in 1951. Dr Fay was a member of the Santa Barbara County Medical Society.

Fischbach, John E., Banning. Died Sept 11, 1995, aged 65. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1957. Licensed in California in 1962. Dr Fischbach was a member of the Riverside County Medical Association.

Forrest, Robert L., Mission Viejo. Died Dec 10, 1995, aged 73. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1946. Licensed in California in 1949. Dr Forrest was a member of the Orange County Medical Association.

Hull, Osman H., Jr, Monterey. Died Oct 13, 1995, aged 77. Graduate of Stanford University School of Medicine, California, 1943. Dr Hull was a member of the Monterey County Medical Society

Jacobs, Herbert N., San Francisco. Died Oct 13, 1995, aged 77. Graduate of University of California, San Francisco, School of Medicine, 1943. Dr Jacobs was a member of the San Francisco County Medical Society.

Jones, Harold W., Oakland. Died Nov 7, 1995, aged 78. Graduate of University of Nebraska College of Medicine, Omaha, 1942. Licensed in California in 1954. Dr Jones was a member of the Alameda-Contra Costa County Medical Association.

Kershner, Richard D., San Jose. Died Sept 24, 1995, aged 72. Graduate of University of Chicago Pritzker School of Medicine, Chicago, Illinois, 1947. Licensed in California in 1953. Dr Kershner was a member of the Santa Clara County Medical Association.

Klasson, William Arthur, Los Gatos. Died Nov 9, 1995, aged 49. Graduate of State University of New York, Syracuse, 1972. Licensed in California in 1973. Dr Klasson was a member of the Santa Clara County Medical Association.

Knudsen, William, Fresno. Died Sept 19, 1995, aged 86. Graduate of University of Illinois College of Medicine, Chicago, 1936. Dr Knudsen was a member of the Fresno-Madera Medical Society.

Miller, Lowell, Palo Alto. Died Oct 6, 1995, aged 75. Graduate of Loyola University of Chicago Stritch School of Medicine, Maywood, Illinois, 1945. Dr Miller was a member of the Santa Clara County Medical Association.

Olson, Elmer, Riverside. Died Oct 10, 1995, aged 90. Graduate of Loma Linda University School of Medicine, California 1934. Licensed in California in 1941. Dr Olson was a member of the Riverside County Medical Associoation.

Rosell, Jon E., Burlingame. Died Oct 21, 1995, aged 74. Graduate of University of Illinois College of Medicine, Chicago, 1948. Licensed in California in 1964. Dr Rosell was a member of the San Mateo County Medical Association.

Smilkstein, Gabriel, Davis. Died Sept 17, 1995, aged 71. Graduate of Rochester School of Medicine, New York, 1953. Dr Smilkstein was a member of the Yolo County Medical Society.

Varney, Dean C., Los Gatos. Died Nov 13, 1995, aged 75. Graduate of Ohio State University College of Medicine, Columbus, 1944. Licensed in California in 1944. Dr Varney was a member of the Santa Clara County Medical Association.

Wong, Donald Gen Ming, San Francisco. Died Oct 23, 1995, aged 64. Graduate of Medical College of Wisconsin, Milwaukee, 1963. Licensed in California in 1964. Dr Wong was a member of the San Francisco County Medical Society.

Wozniak, John M., Sacramento. Died Nov 3, 1995, aged 80. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania 1942. Licensed in California in 1946. Dr Wozniak was a member of the Sacramento-El Dorado County Medical Society.

Denver Medical Society

DiLorenzo, Pasquale Anthony, Denver. Died Aug 27, 1995, aged 58. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1963. Licensed in Colorado in 1966. Dr DiLorenzo was a member of the Denver Medical Society.

Klenk, Eugene Leslie, Denver. Died Nov 7, 1995, aged 65. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania 1962. Licensed in Colorado in 1980. Dr Klenk was a member of the Denver Medical Society.

New Mexico Medical Society

Conklin, Coursen B., Albuquerque. Died Oct 12, 1995, aged 74. Graduate of George Washington University School of Medicine, Washington, District of Columbia, 1945. Licensed in New Mexico in 1959. Dr Conklin was a member of the Greater Albuquerque Medical Association.

Cummings, Michael J., Los Alamos. Died Sept 24, 1995, aged 79. Graduate of University of New Mexico School of Medicine, Albuquerque, 1978. Licensed in New Mexico in 1986. Dr Cummings was a member of the Los Alamos County Medical Society.

Goldminz, Abraham E., Carlsbad. Died Sept 28, 1995, aged 68. Graduate of Chicago Medical School, North Chicago, Illinois 1952. Licensed in New Mexico in 1953. Dr Goldminz was a member of the Eddy County Medical Society.

Storrs, Bruce D., Albuqueruqe. Died Oct 16, 1995, aged 82. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, Canada. Licensed in New Mexico in 1967. Dr Storrs was a member of the Greater Albuquerque Medical Association.

Articles

Driving and Dementia
California's Approach to a Medical and Policy Dilemma

DAVID B. REUBEN, MD, *and* PEGGY ST GEORGE, *Sacramento, California*

The cognitive impairment that defines dementia is thought to place affected persons at increased risk for unsafe driving. Nevertheless, many persons with dementia continue to drive after the onset of their illness. Since 1988 California physicians have been required to report older persons with Alzheimer's disease and related disorders to their local health departments, information that is then reported to the Department of Motor Vehicles (DMV). To reevaluate how it acts on this information, the DMV convened an interdisciplinary panel of experts and modified its policies regarding drivers with dementia. As revised, the driver's licenses of persons with moderate or advanced dementia will be revoked without further testing. Persons with early or mild dementia will have the opportunity to demonstrate the capacity to drive through a reexamination process. In this manner, the California DMV hopes to balance the need for public safety and with the preservation of personal independence of persons with dementia.

(Reuben DB, St George P: Driving and dementia—California's approach to a medical and policy dilemma. West J Med 1996; 164:111-121)

Demographic trends indicate that the number of Americans aged 65 years and older will increase dramatically over the next several generations, particularly as the "baby boomers" enter this age group in the early 21st century.[1] Because Alzheimer's disease and other dementing disorders are age-associated, the number of older persons with these diseases will rise concomitantly.[2,3] Although the consequences of dementia engender enormous health care and economic burdens, a particular aspect of the disorder, the effect on the ability to drive safely, has been a prominent medical and public health issue. From a medical perspective, the cognitive impairment that defines dementia with hallmark features of memory loss, visual-spatial disturbance, and impaired judgment is likely to place a person with dementia at an increased risk for unsafe driving. Other more subtle impairments, such as poor divided attention ability, poor selective focused attention,[4] and visual field limitations[5] that are characteristic of patients with Alzheimer's disease, may contribute to or aggravate this risk.

The possible risk of unsafe driving by drivers with dementia has been substantiated in most,[6-9] though not all,[10] retrospective studies that have shown higher rates of motor vehicle crashes and in performance-based studies that have shown poor driving skills on road tests.[4,11,12] Although the precise magnitude of risk incurred by a driver who has dementia cannot be estimated from the existing literature, this risk is likely to be substantial. It has been reported that 33% of demented persons who were still driving had motor vehicle crashes or moving violations within the previous six months.[8]

Nevertheless, older drivers with dementia continue to drive after the onset of their illness. Again, precise estimates of the prevalence of driving among demented persons are not available because of study limitations. Published data, however, seem to suggest that at least a substantial minority, and perhaps a majority, of persons with dementia continue to drive after the onset of their illness, particularly early in the disease. Of those who were driving at the time of diagnosis in the previously mentioned series, 73% continued to drive for at least a year, and these persons drove for a median of 24 months.[8] As the disease progresses, the prevalence of driving declines substantially, although patients with Alzheimer's disease may drive longer than do those with dementia from other causes.[6,8]

Thus, it cannot be assumed that a demented person will invariably be cognizant enough of the risks to voluntarily cease driving. Nor can family members be uniformly relied on to persuade a demented person to refrain from driving.[13] In some cases, a demented person has been the sole driver for the family. In other cases, current and premorbid relationships between family members preclude enforcement of a family-generated restriction.

Some experts have recommended that medical determinations by physicians should guide the decision regarding driver competency. For example, the most

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Reprint requests to Peggy St George, Program Manager, Dept of Motor Vehicles, 2415 First Ave, Sacramento, CA 95814.

ABBREVIATIONS USED IN TEXT

DME = driver medical evaluation
DMV = Department of Motor Vehicles

recent American Medical Association guidelines on driving state that "once the presence of dementia is established and it is demonstrated that a patient is at risk of making errors in judgment likely to affect the ability to drive safely, an individual should not drive again."[14(p33)] Others have urged that the diagnosis of dementia should be followed by a formal evaluation designed specifically to test driving competence.[15,16] It has also been suggested that the physician's role is to identify drivers who have dementia (including reporting to the state department of motor vehicles, when appropriate) and then to allow the department of motor vehicles to make the decision whether to restrict or revoke the driving privilege.[17]

California's Law and Policy

In California in 1988, Health and Safety Code section 410 added Alzheimer's disease and related disorders to the list of conditions that physicians are required to report (using a Confidential Morbidity Report form) to their local health departments, which then forward this information to the California Department of Motor Vehicles (DMV). The guidelines for reporting, which were modified slightly in 1990, are specific, and failure to report may lead to liability for the physician if the patient becomes involved as a driver in a crash. Reporting means that the person with dementia is required to be reexamined by a hearing officer and to submit to further tests, which usually included vision, knowledge, and driving examinations. Based on the results of these examinations as well as a physician-completed written driver medical evaluation (DME) form, the DMV could allow the driver to continue driving unrestricted, put the driver on probation, restrict driving, or revoke or suspend the driver's license. The basis for deciding among these options has not always been clear, however.

As part of a process to reevaluate the DMV's policy toward drivers with physical and mental impairments, in 1992 the DMV began systematically reviewing and modifying its method of evaluating drivers with dementia. The DMV was concerned that the identification and evaluation of drivers with dementia were not being conducted in a uniform manner. Both the process of this evaluation and its results are of interest. To reevaluate its current policy relating to dementia, the DMV convened a panel of experts that met four times over a six-month period. The panel* was diverse in composition and included physicians, DMV representatives, and representatives of consumer groups. Physician panel members included neurologists, a geriatric psychiatrist, a public health official, and a geriatrician. Each of these members had experience in managing dementia, and several had considerable experience in dealing with driving impairments. The DMV representatives included driver-safety hearing officers and driver-control-policy research staff and managers. Representatives from the Alzheimer's Association participated on behalf of consumers, representing caregivers. For each type of dementia, the physicians in the panel reviewed published literature and drew on clinical experience to define functional impairments, driving-related impairments, and other modifying factors to consider. The DMV representatives shared their research data and personal experiences in examining drivers with dementia and also provided a series of licensing options, ranging from no action to revocation, that the group could choose from. Based on deliberations of the panel, a new physician-completed DME form for dementia (Figure 1) and a new reporting form for nonphysicians (including other health professionals and lay persons) (Figure 2) were created. The goal of the new forms is to provide as precise information as possible regarding the severity of dementia. Finally, a new schema for evaluating drivers with dementia was created (Figure 3).

The rationale behind the schema and its operation merit further explanation. There was uniform agreement by the panel members that persons with moderate or advanced (severe) dementia (Table 1)[18] should not be driving. Thus, when a physician's initial report indicates that dementia is moderate or advanced, the demented person's driver's license will be revoked immediately without further testing. If the physician's report indicates that the dementia is mild or the diagnosis is unclear, a DME form will be sent to the driver's physician for completion. Similarly, if the report has been generated by a family member, friend, day-care agency, or other person (such as a law enforcement official or DMV field officer), a DME form is sent to the patient's physician. Because persons with dementia often are treated by more than one physician, the question arises

TABLE 1.—*Classification of Severity of Dementia**

Severity	*Example*
Mild	Judgment is relatively intact, but work or social activities are substantially impaired
Moderate	Independent living is hazardous, and some degree of supervision is necessary
Severe	Activities of daily living are so impaired that continual supervision is required

*From the American Psychiatric Association.[18]

*Dementia Panel members: *DMV staff*: Patti Caraska, Allan Cates, Joan Eubanks, Annette Heck, Mary Hurtado, Mary Janke, PhD, Kathy Kelly, Barbara Lancara, Peggy St George, and Gilbert Von Studnitz. *DMV Medical Advisory Board*: David B. Reuben, MD, and Jerry Zarriello, MD. *Consumer groups*: John Davidson, President, Sacramento Chapter, Alzheimer's Association. *California Alzheimer's Disease Program*: James Howard. *Physician and nursing experts*: John Bissel, MD, Chief, Department of Neurology, Kaiser-Permanente, Sacramento; L. Jaime Fitten, MD, Chief, Geropsychiatry, Veterans Affairs Medical Center, Sepulveda, and University of California, Los Angeles (UCLA) School of Medicine; Michael Mahler, MD, Associate Professor of Neurology, UCLA School of Medicine; and Maxine Verna, RN, PhD, Program Coordinator, Alzheimer's Disease Diagnostic and Treatment Center, Sacramento, California.

A Public Service Agency

PHYSICIAN *RETURN FORM TO:*

DRIVER MEDICAL EVALUATION

(Medical information is CONFIDENTIAL under Section 1808.5 CVC)

BY THE INDICATED DATE:

NAME (LAST, FIRST, MIDDLE) | DRIVER LICENSE NO. | BIRTH DATE | FIELD FILE

STREET ADDRESS | CITY | ZIP | PATIENT'S DAYTIME OR HOME PHONE NO. ( )

The Department of Motor Vehicles' records indicate your patient may have a condition that could affect the safe operation of a motor vehicle. With your assistance, we hope to resolve the matter with a minimum of inconvenience to all concerned.

Your experience and knowledge of the patient's condition, results of medical examinations, and treatment plans, will be of great value in assisting the department to determine a proper licensing decision. PLEASE ANSWER ALL QUESTIONS on this form that are applicable to your patient's condition. You may furnish a narrative report if you prefer, but please include all information pertinent to your patient. *The department has sole responsibility for any decision regarding the patient's driving qualifications and licensure. The department will also consider non-medical factors in reaching a decision.*

DIAGNOSIS

DIAGNOSIS (If this patient has a disorder characterized by a lapse of consciousness or dementia, please complete the information on page 2.)

DO YOU NEED TO SEE YOUR PATIENT AT REGULAR INTERVALS? IF YES, HOW OFTEN?

☐ Yes ☐ No

PROGNOSIS

IS THE CONDITION

☐ improving ☐ stable ☐ worsening or deteriorating ☐ subject to change

MANIFESTATIONS:

(PRESENT)

(PAST)

MEDICAL REGIMEN

HOW LONG HAS THIS PERSON BEEN YOUR PATIENT? | DATE OF LAST EXAMINATION

IS YOUR PATIENT UNDER A CONTROLLED MEDICAL PROGRAM?

☐ Yes ☐ No

HOW LONG HAS CONTROL BEEN MAINTAINED?

IS THE PATIENT ADHERING TO THE MEDICAL REGIMEN? IF NO, PLEASE EXPLAIN:

☐ Yes ☐ No

MEDICATIONS

LIST THE MEDICATIONS PRESCRIBED. PLEASE INCLUDE DOSAGE AND FREQUENCY OF USE

WOULD THE SIDE EFFECTS FROM THE PRESCRIBED MEDICATIONS INTERFERE WITH THE SAFE OPERATION OF A MOTOR VEHICLE?

☐ Yes ☐ No If yes, please describe:

PLEASE ANSWER QUESTIONS ON THE NEXT PAGES

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Figure 1.—An example of the driver medical evaluation form for reporting a possible case of dementia is shown. *(Continued on the following three pages)*

LAPSE OF CONSCIOUSNESS DISORDER

PLEASE IDENTIFY THE LAPSE OF CONSCIOUSNESS DISORDER BEING REPORTED *(Type of seizure, nocturnal, isolated, syncope, blackouts, etc.)*

DATE(S) OF EPISODE(S) IN THE PAST THREE YEARS

DATE OF ONSET, IF KNOWN

DATE AND TIME OF LAST EPISODE

Please indicate the impairments identified below that are **presently** shown by your patient

	YES	NO	UNCERTAIN
Sporadic loss of conscious awareness	☐	☐	☐
Loss of consciousness	☐	☐	☐
Impaired motor function	☐	☐	☐
EFFECTS AFTER EPISODE			
Confusion	☐	☐	☐
Diminished concentration	☐	☐	☐
Diminished judgment	☐	☐	☐
Memory loss	☐	☐	☐

If medication is taken to control seizures, are the serum levels recorded? ☐ Yes ☐ No

Are the serum levels medically acceptable? ☐ Yes ☐ No

DEMENTIA OR COGNITIVE IMPAIRMENTS

☐ **Alzheimer's Disease**

☐ **Other Dementia** (Please describe the type of dementia below, e.g., multi-infarct, metabolic, post-traumatic.)

HISTORY OF DISEASE, RESULTS OF TESTING, ETC.

Rate the degree of cognitive impairments, where applicable, to the condition being reported. To aid in determining the overall degree of severity, please refer to the definitions below.

	NONE	MILD	MODERATE	SEVERE	UNCERTAIN
Memory Loss	☐	☐	☐	☐	☐
Diminished Judgment	☐	☐	☐	☐	☐
Impaired Attention	☐	☐	☐	☐	☐
Impaired Language Skills	☐	☐	☐	☐	☐
Impaired Visual Spatial Skills	☐	☐	☐	☐	☐
Impulsive Behavior	☐	☐	☐	☐	☐
Problem Solving Deficits	☐	☐	☐	☐	☐
Loss of Awareness of Disability	☐	☐	☐	☐	☐
OVERALL DEGREE OF IMPAIRMENT		☐	☐	☐	

Mild: Judgment is relatively intact but work or social activities are significantly impaired. Ability to safely operate a motor vehicle may or may not be impaired.

Moderate: Independent living is hazardous and some degree of supervision is necessary. The individual is unable to cope with the environment and driving would be dangerous.

Severe: Activities of daily living are so impaired that continual supervision is required. This person is incapable of driving a motor vehicle.

HISTORY OF OTHER MEDICAL CONDITIONS

	YES*	NO
Diabetes and/or hypoglycemic episodes	☐	☐
Stroke	☐	☐
Dizziness from frequent headaches	☐	☐
Eye disorders not correctable by lenses	☐	☐
Cardiovascular diseases or disorders	☐	☐
Kidney disease	☐	☐
Musculoskeletal impairments	☐	☐
Head, neck, or spinal injury	☐	☐
Psychiatric disorder(s)	☐	☐
Emotional disorder(s)	☐	☐
Alcohol abuse	☐	☐
Drug abuse	☐	☐
Other, please describe	☐	☐

LEVELS OF FUNCTIONAL IMPAIRMENTS

Functional impairments that may affect safe driving ability. Please check where applicable.

	MILD	MODERATE	SEVERE
Visual neglect	☐	☐	☐
Loss of upper extremity motor control .. ☐ Left side ☐ Right side	☐	☐	☐
Loss of lower extremity motor control .. ☐ Left side ☐ Right side	☐	☐	☐

IN YOUR OPINION, DOES YOUR PATIENT'S MEDICAL CONDITION AFFECT SAFE DRIVING?

☐ Yes ☐ No ☐ Uncertain

WOULD ADAPTIVE DEVICES AID YOUR PATIENT IN COMPENSATING FOR HIS/HER DISABILITY?

☐ Yes ☐ No ☐ Uncertain

IF YES, PLEASE DESCRIBE

WOULD YOU RECOMMEND A DRIVING TEST BE GIVEN BY DMV?

☐ Yes ☐ No ☐ Uncertain

*Please provide additional information on page 4 for any condition in which "yes" was checked. Please include onset date, medications not identified on page 1, and the number of incidents or episodes if applicable.

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DRIVER'S ADVISORY STATEMENT

Medical information is required under the authority of Divisions 6 and 7 of the California Vehicle Code. Failure to provide the information is cause for refusal to issue a license or to withdraw the driving privilege.

All records of the Department of Motor Vehicles, relating to the physical or mental condition of any person, are confidential and not open to public inspection (California Vehicle Code Section 1808.5). Information used in determining driving qualifications is available to you and/or your representative with your signed authorization.

The department has sole responsibility for any decision regarding your driving qualifications and licensure. The department will also consider non-medical factors in reaching a decision.

MEDICAL INFORMATION AUTHORIZATION
(Valid for three years)

PHYSICIAN, HOSPITAL, OR MEDICAL FACILITY *(NAME AND ADDRESS)*

DATE	MEDICAL RECORD/PATIENT FILE NUMBER

I hereby authorize my physician or hospital to answer any questions from the Department of Motor Vehicles, or its employees, relating to my physical or mental condition, and/or drug and/or alcohol use or abuse, and to release any related information or records to the Department of Motor Vehicles or its employees. Any expense involved is to be charged to me and not to the Department of Motor Vehicles.

I hereby authorize the Department of Motor Vehicles to receive any information relating to my physical or mental condition, and/or drug and/or alcohol use or abuse, and to use the same in determining whether I have the ability to operate a motor vehicle safely.

NOTE: You may wish to make a copy of the completed Driver Medical Evaluation for your records.

PHYSICIAN'S SIGNATURE

PHYSICIAN'S SIGNATURE	PHYSICIAN'S NAME *(PRINTED)*	DATE
X		
CLASSIFICATION OR SPECIALTY	MEDICAL LICENSE NUMBER	TELEPHONE NUMBER
		( )

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ADDITIONAL COMMENTS TO BE COMPLETED BY PHYSICIAN
(If comments are added, please sign again below.)

PHYSICIAN'S SIGNATURE
X

DS 326 (REV 6/93)

A Public Service Agency

REPORT OF DRIVER WITH DEMENTIA

Please complete this form if you wish the Department of Motor Vehicles to review the driving qualifications of a person who may have dementia. You may request that your name or agency not be revealed to the individual being reported. Confidentiality may be requested at the bottom of this form.

Vehicle Code Section 1808.5 ensures that all records received by the department relating to the physical or mental condition of any person are confidential and not open to public inspection.

NAME OF INDIVIDUAL BEING REPORTED	DRIVER LICENSE NO. *(IF AVAILABLE)*	BIRTH DATE
ADDRESS OF INDIVIDUAL BEING REPORTED	CITY	ZIP CODE

Based on your interactions with the individual being reported, please rate the person's degree of impairment.

	NONE	MILD	MODERATE	SEVERE	UNCERTAIN
Memory Loss	☐	☐	☐	☐	☐
Deterioration in Judgment	☐	☐	☐	☐	☐
Inability to Maintain Attention	☐	☐	☐	☐	☐
Impulsive Behavior	☐	☐	☐	☐	☐
Inability to Perceive Serious Situations Accurately	☐	☐	☐	☐	☐
Confusion	☐	☐	☐	☐	☐

Do you believe that this person is unsafe to operate a motor vehicle? ☐ Yes ☐ No ☐ Uncertain
If yes, please describe.

Does this person have difficulty with daily care activities? For example, does the person have difficulty cooking meals, balancing a checkbook, maintaining personal hygiene? ☐ Yes ☐ No ☐ Uncertain
If yes, please describe.

The DMV will keep your name confidential if you request. However, it will be necessary for you to sign this form in order for the department to investigate this matter.

Do you wish to keep your name/agency from the person being reported? ☐ Yes ☐ No

This information is provided by: ☐ Family Member ☐ Day Care Agency ☐ Friend ☐ Neighbor ☐ Other

NAME OF REPORTER	TELEPHONE NUMBER
	( )

PLEASE RETURN THIS FORM TO YOUR LOCAL DRIVER SAFETY OFFICE

THE REVERSE SIDE OF THIS FORM EXPLAINS THE PROCEDURES DMV FOLLOWS WHEN EVALUATING A DRIVER REPORTED WITH DEMENTIA

DS 699 (NEW 6/93)

Figure 2.—An example of the form for reporting by nonphysicians of a possible case of dementia is shown. *(Continued on the following page.)*

PROCEDURES DMV FOLLOWS WHEN EVALUATING A PERSON REPORTED WITH DEMENTIA

Reporting a Relative, Friend, or Client to DMV

A Notice of Reexamination will be mailed to the person you have reported. The notice tells the person that in the interest of his/her personal safety and the safety of others on the road, the DMV has determined it necessary to review the person's driving qualifications.

Review of Medical Information

The reported person will be sent a Driver Medical Evaluation form along with the Notice of Reexamination. The person is requested to have the physician, most familiar with his/her medical history, complete the form. The person is informed that the Driver Medical Evaluation must be returned to DMV within 20 days or the driving privilege will automatically be suspended. The person is also informed that failure to appear at the scheduled reexamination will result in suspension of the driving privilege.

The Reexamination Interview

The reported person will be given a written knowledge test on the rules of the road prior to the reexamination interview. The reexamination interview will be held if the person passes the knowledge test. If the person does not pass the written test, the person's driving privilege is suspended or revoked.

The reexamination interview gives the person the opportunity to discuss his/her medical condition with a DMV representative for purposes of establishing the person's ability to safely operate a motor vehicle. The DMV representative will ask the person questions to determine memory deterioration, awareness, orientation, attention, and judgment. The representative will be observant of the person's coordination and adaptation to the environment, as well.

Further Testing

The DMV representative interviewing the reported individual will determine if the person should be given a driving test. This decision is based on the information provided by the reported person, medical documentation, and the results of the written examination. A driving test is not given if the evidence indicates the reported individual may be unable to safely operate a motor vehicle. If that is apparent, the driving privilege is then suspended or revoked.

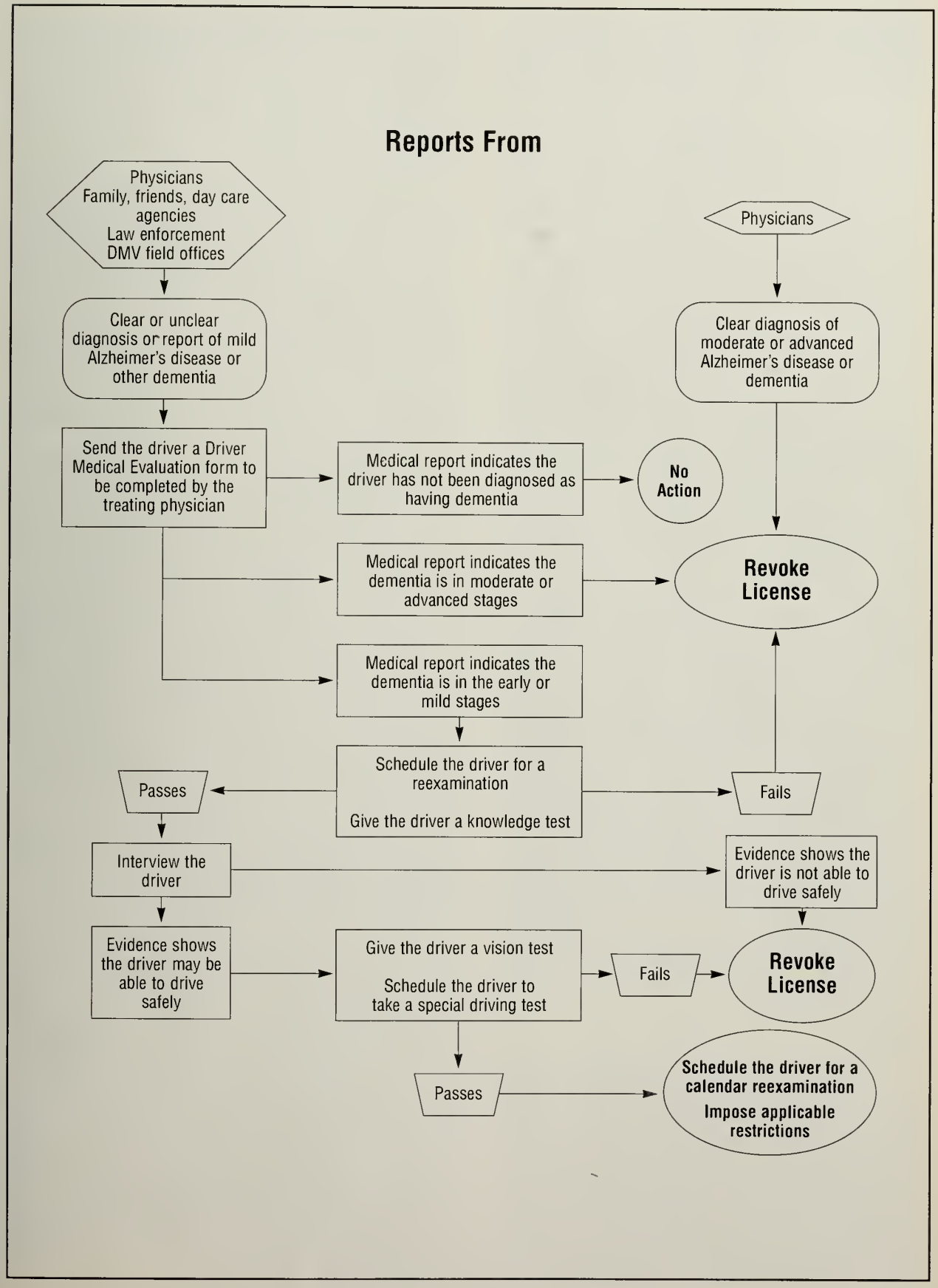
The Driving test

The driving test given to individuals reported with dementia takes 30–45 minutes. The examiner will be looking for the person's ability to concentrate, recall multiple instructions, execute them safely, and possibly find a location that should be familiar to the person (church, doctor, pharmacy, home, store, etc.). The examiner will be watching for signs of mental confusion, perceptual misjudgment, and/or impulsiveness.

DMV Decision

At the conclusion of the driving test, the examiner will document the person's areas of strengths and weaknesses. The interviewer will review the results of the driving test. These results, in combination with the medical documentation, the reported person's testimony, and any testimony of witnesses accompanying the reported person, lead to the licensing decision. If the evidence shows the reported individual is capable of safely operating a motor vehicle, he/she will be allowed to continue to drive. The person will be required to return to DMV again within 3–12 months for another reexamination interview. This allows the department to monitor any deterioration of the reported individual's medical condition as it relates to driving.

DS 699 (NEW 6/93)


Reports From
Physicians
Family, friends, day care agencies
Law enforcement
DMV field offices
Physicians
Clear or unclear diagnosis or report of mild Alzheimer's disease or other dementia
Clear diagnosis of moderate or advanced Alzheimer's disease or dementia
Send the driver a Driver Medical Evaluation form to be completed by the treating physician
Medical report indicates the driver has not been diagnosed as having dementia
No Action
Medical report indicates the dementia is in moderate or advanced stages
Revoke License
Medical report indicates the dementia is in the early or mild stages
Schedule the driver for a reexamination
Give the driver a knowledge test
Passes
Fails
Interview the driver
Evidence shows the driver is not able to drive safely
Evidence shows the driver may be able to drive safely
Give the driver a vision test
Schedule the driver to take a special driving test
Fails
Revoke License
Passes
Schedule the driver for a calendar reexamination
Impose applicable restrictions

as to which physician should receive the DME form. Although the physician who is most familiar with the driver's dementia would be the best one to complete the DME form, the choice of physician to receive the form is the driver's option. The DME form asks physicians to rate specific cognitive and behavioral disturbances and to provide an assessment of the overall degree of impairment. Definitions of mild, moderate, and severe impairment are provided in Table 1. If this medical report indicates moderate or advanced dementia, the license is revoked. On the other hand, if the medical report indicates that the dementia is in early or mild stages, the driver is scheduled for reexamination by the DMV.

This DMV reexamination is conducted sequentially, beginning with a standard knowledge test (written or oral), followed by an interview with a driver-safety hearing officer, a vision test, and a special driving test. Failure on any of the tests, except vision, will automatically lead to revoking the license. During the interview, the hearing officer asks questions that focus on memory, awareness, orientation, attention, and adaptation. Sample questions are provided in the DMV-published *Driver Safety Manual*, and standards for considering the interview to be unsatisfactory have been established. The special driving test differs from the ordinary driving test in that it is longer (average time, 30 to 45 minutes versus 15 to 20 minutes, maximum) and requires a set of specific road instructions, including complicated commands and maneuvers, that might simulate difficult situations (for example, talking to distract the driver). It is longer in duration to determine if fatigue causes driving skills to deteriorate after 20 or 30 minutes on the road, but is not more difficult than a regular driving test. If a demented driver passes all of these tests, he or she is scheduled for a calendar reexamination—that is, the driver is reevaluated with the same battery of tests in 6 to 12 months, the exact timing depending on performance on the current examination and expected progression of the disease as indicated by the physician's report on the DME form.

At each step in the process, the driver is entitled to an appeal within the DMV. The driver can also appeal through the state court system once administrative appeal within the DMV has been exhausted. For drivers who lose their driving privileges, each of the 22 driver-safety offices in California provides lists of local alternative transportation.

Discussion

Despite appearing relatively straightforward, a number of questions arise about the implementation of the DMV's policy. First, what happens if a driver who has been reported obtains a second opinion that contradicts the original diagnosis? In this situation, the driver-safety hearing officer reviews both reports thoroughly. If there was a misdiagnosis that can be clearly explained, such as medication toxicity, a resolving delirium, or a reversible cause of dementia, there may be no need to retest the driver. A previous decision of revocation can be set aside. When the discrepancy cannot be resolved so easily, the hearing officer considers the credentials of the physician (such as medical specialty) and the relationship of the physician with the patient (for instance, how long the physician has been treating the driver). A DMV reexamination (as described earlier) may be necessary to evaluate the person's driving knowledge and skill before a decision can be rendered.

Second, do physicians have to re-report a driver with dementia if the driver's mental state deteriorates? This is being addressed through the regulatory process that is currently taking place in California. Health and Safety Code section 410, however, protects physicians from civil and criminal liability for subsequent re-reporting as well as the initial reporting. As mentioned earlier, the DMV periodically monitors all drivers who have been reported with dementia and who have been evaluated and are allowed to continue driving. If a driver's dementia is deteriorating rapidly and he or she is not scheduled to return to the DMV for several months, the physician may want to re-report the driver.

Although this process may seem arbitrary, it reflects the best clinical judgment of physicians who have considerable experience with the disorder and the experiences of the governmental agency that knows the most about driving. The physicians have identified as precisely as possible subgroups of demented patients who should not be driving under any circumstances, thereby reducing the burden on the DMV, which is charged with evaluating drivers with dementia who have been reported by their physicians. This strategy recognizes, however, that some drivers with early dementia may still be capable of driving and provides them the opportunity to demonstrate their knowledge and skills in a performance-based setting. It also does not ask DMV officers to make medical judgments about the competency of a patient to drive. Rather, their judgments are based solely on the driver's ability to pass the evaluations. The process, therefore, draws on the unique and complementary skills of physicians, who are the most capable of providing medical information, and the DMV, which is the most capable of evaluating driving skills.

Despite care spent in developing these guidelines, this system for evaluating older drivers with dementia is imperfect. Some physicians will be unable to accurately classify their patients' dementias and associated cognitive impairments as mild, moderate, or severe. Although physicians may indicate on the form that standardized instruments were used in making these determinations, most will rely on subjective judgments. Undoubtedly, some incorrect decisions regarding licensure may be made despite the best efforts of both physicians and the DMV. As new performance-based tests of driving skills, including useful field of view,[19] simulated driving devices,[20] and other performance-based measures are developed, the reliability in making these decisions will likely improve. Of course, the system cannot prevent drivers with dementia from driving despite having their licenses revoked.

For physicians, a number of questions arise about the effect of these new guidelines on reporting and physician-patient relationships. Because physicians who report severe or moderate dementia may know that the patient's license will be taken away, is the physician in effect taking the license away? Will the new protocol lead to underreporting or reporting of dementia as "mild" when it is actually "moderate" or "severe" because of fears that the person's license will be automatically revoked? Since the 1988 rules were implemented, physicians have been concerned about the effect of reporting on the physician-patient relationship, and the incidence of reporting has been lower than anticipated, even among those who care for many demented patients. Many physicians think that reporting patients, especially those with mild or moderate dementia, will jeopardize the physician-patient relationship, perhaps permanently. These concerns are of particular interest because the effects of the reporting requirement and subsequent restriction of licenses have not yet been rigorously evaluated. It is also possible that patients who are declining in cognitive capacities may avoid seeking care because of the threat of losing their driver's licenses. If so, the treatment of possibly reversible causes of cognitive decline might be delayed.

Nevertheless, California physicians are obligated to follow current state law. Recognizing this reporting requirement, the DMV has attempted to provide a clear policy for the actions that will be taken subsequent to the DMV's learning that a driver has a diagnosis of dementia. It has used the best available information to identify and revoke the licensure of high-risk drivers with dementia, yet permit continued licensure of mildly demented patients who may still be able to drive safely. In doing so, the DMV has developed guidelines to improve its process in making consistent decisions based on functional impairments and in conforming with the Americans with Disabilities Act to prevent discrimination. Once implemented, the California plan would benefit from being evaluated systematically, including the assessment of crash rates of those who are permitted to retain their licenses and psychosocial effects on those who have lost their licenses because of dementia. For now, however, the strategy outlined herein appears to provide the best compromise in efforts to preserve personal independence while maintaining public safety.

REFERENCES

1. American Association of Retired Persons (AARP) and Administration on Aging—A Profile of Older Americans (Brochure PF3049 [1294]-D996). Washington, DC, AARP, 1994

2. Evans DA, Funkenstein HH, Albert MS, et al: Prevalence of Alzheimer's disease in a community population of older persons—Higher than previously reported. JAMA 1989; 262:2551-2556

3. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A: A population-based study of dementia in 85-year-olds. N Engl J Med 1993; 328:153-158

4. Fitten LJ, Perryman KM, Wilkinson CJ, et al: Alzheimer and vascular dementias and driving—A prospective road and laboratory study. JAMA 1995; 273:1360-1365

5. Steffes R, Thralow J: Visual field limitation in the patient with dementia of the Alzheimer's type. J Am Geriatr Soc 1987; 35:198-204

6. Friedland RP, Koss E, Kumar A, et al: Motor vehicle crashes in dementia of the Alzheimer type. Ann Neurol 1988; 24:782-786

7. Lucas-Blaustein MJ, Filipp L, Dungan C, Tune L: Driving in patients with dementia. J Am Geriatr Soc 1988; 36:1087-1091

8. Gilley DW, Wilson RS, Bennett DA, et al: Cessation of driving and unsafe motor vehicle operation by dementia patients. Arch Intern Med 1991; 151:941-946

9. Dubinsky RM, Williamson A, Gray CS, Glatt SL: Driving in Alzheimer's disease. J Am Geriatr Soc 1992; 40:1112-1116

10. Waller PF, Trobe JD, Olson PL, Teshima S, Cook-Flannagan C: Crash Characteristics Associated With Early Alzheimer's Disease. Presented at the 37th Annual Proceedings, Association for the Advancement of Automotive Medicine, San Antonio, Texas, November 1993

11. Hunt L, Morris JC, Edwards D, Wilson BS: Driving performance in persons with mild senile dementia of the Alzheimer type. J Am Geriatr Soc 1993; 41:747-753

12. Odenheimer G, Beaudet M, Jette AM, Albert MS, Grande L, Minaker KL: Performance-based driving evaluation of the elderly driver: Safety, reliability, and validity. J Gerontol 1994; 49:M153-M159

13. Persson D: The elderly driver: Deciding when to stop. Gerontologist 1993; 33:88-91

14. Doege TC, Engelberg AL (Eds): Medical Conditions Affecting Drivers. Chicago, Ill, American Medical Association, 1986

15. Donnelly RE, Karlinsky H: The impact of Alzheimer's disease on driving ability: A review. J Geriatr Psychiatry Neurol 1990; 3:67-72

16. Drachman DA: Who may drive? Who may not? Who shall decide? (Editorial) Ann Neurol 1988; 24:787-788

17. Reuben DB: Dementia and driving. J Am Geriatr Soc 1991; 39:1137-1138

18. Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised: DSM-III-R. Washington, DC, American Psychiatric Association, 1987

19. Ball K, Owsley C: Identifying correlates of accident involvement for the older driver. Human Factors 1991; 33:583-595

20. Keyl P, Rebok G, Bylsma F, Rodman A: Simulated driving performance in Alzheimer's patients in relation to accident involvement (Abstr). Gerontologist 1991; 31:155

Articles

Human Immunodeficiency Virus Disease in California

Effects of the 1993 Expanded Case Definition of the Acquired Immunodeficiency Syndrome

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On January 1, 1993, the case definition of the acquired immunodeficiency syndrome (AIDS) in adults and adolescents used for monitoring the AIDS epidemic in California was expanded to include persons infected with the human immunodeficiency virus (HIV) with CD4 T-lymphocyte counts of less than 200 $\times$ 10^6 per liter (<200 per mm^3), pulmonary tuberculosis, recurrent pneumonia, or invasive cervical cancer. To assess the implications of this revision on AIDS case reporting in California, we compared cases reported through the end of 1994 based on 1 or more of the 4 new AIDS-defining conditions added in 1993 to cases reported based on pre–1993 AIDS-defining opportunistic infections and cancers. The 4 new conditions included in the 1993 expanded AIDS case definition accounted for a 23% increase in cumulative AIDS cases reported in California by the end of 1993, a 170% increase in the number of cases reported during 1993, and an 88% increase in the number of patients with AIDS living at the end of 1993. The number of cases reported in 1993 (19,629) was 124% more than that reported in 1992 (8,780) and 69% more than that reported in 1994 (11,587). The proportion of cases among women, injection-drug users, and African Americans also increased as a result of this change in the case definition. The expansion of the case definition may have resulted in a peak or plateau in the AIDS incidence in California because of reporting earlier in the HIV disease progression. The expanded case definition has enhanced the usefulness of AIDS surveillance data for targeting secondary prevention efforts, but more behavioral and HIV serosurveys are still needed to adequately target primary HIV prevention efforts.

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As we enter the 14th year since the recognition of the acquired immunodeficiency syndrome (AIDS), the need to monitor the scope of and trends in the human immunodeficiency virus (HIV) epidemic continues. These data are crucial for identifying targets for primary and secondary interventions, evaluating prevention efforts, allocating resources for HIV-related clinical and social services, planning for the future need for HIV-related services, and educating the public. The cornerstone of our surveillance efforts has been the confidential reporting of persons diagnosed with AIDS—that is, HIV-infected persons with one or more specified opportunistic infections or malignant neoplasms, or depressed levels of CD4 T lymphocytes. Case-surveillance data for AIDS have provided a consistent, population-based picture of the scope of and trends in HIV disease.

In California, an estimated 130,000 to 175,000 residents (1 in 200 to 250) are currently infected with HIV, or about 17% of the nation's HIV-infected population.[1] Major modes of HIV transmission have been identified (most from male-to-male sexual contact), as well as the existence of multiple subepidemics among regions, men having sex with men, injection-drug users, ethnic minorities, and heterosexual women and men.[2,3] Infection with HIV was estimated to be the leading cause of years of potential life lost before age 65 in California in 1993.[4]

To improve the sensitivity of AIDS case-surveillance data, the Centers for Disease Control and Prevention (CDC) has serially revised the case definition of AIDS.[5] In the most recent revision, which became effective January 1, 1993, HIV-infected adults and adolescents with CD4 T-lymphocyte counts of less than 200 $\times$ 10^6 per liter (<200 per mm^3), or a CD4 T-lymphocyte per-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control and Prevention
CDHS = California Department of Health Services
CI = confidence interval
HIV = human immunodeficiency virus
OR = odds ratio

centage of total lymphocytes of less than 0.14, were added as reportable AIDS cases.[6] The expansion also included HIV-infected adults and adolescents with pulmonary tuberculosis, recurrent pneumonia, or invasive cervical cancer. These additions were intended to be consistent with standards of medical care for HIV-infected persons, to include persons with life-threatening conditions of major public health importance in the HIV epidemic, and to simplify the AIDS case reporting process.[7] The CDC had last changed the AIDS case definition in 1987; among California AIDS cases diagnosed after the August 31, 1987, implementation of this revision and reported through 1988, 17% met only the new criteria.[8,9] This revision also increased the proportion of cases among injection-drug users.[9]

Nationally, the expanded definition was expected to increase the number of persons reported with AIDS during 1993 by 75%.[10,11] In California, 8,000 to 10,000 reported cases were expected during 1993 to meet the expanded definition criteria, in addition to the 9,000 cases expected to meet the previous case definition. Given this large anticipated increase in the number of cases, state and local AIDS surveillance programs developed strategies to maintain and improve the security, completeness, accuracy, and timeliness of case reporting. We describe in this article the effects of the 1993 expanded AIDS case definition on AIDS case reporting in California.

Methods

Health care professionals in California are required to confidentially report persons with AIDS to local health departments.[12] Information on patient demographics, clinical status, and modes of exposure to HIV are recorded on standardized forms and forwarded to the California Department of Health Services (CDHS).

Under a cooperative agreement with the CDC, CDHS staff extensively trained local health departments in expanded case reporting. Before the January 1, 1993, implementation date, all local health departments had been informed of the expanded case definition criteria, and most had also informed health care professionals. Local health departments were advised to do the following:

- Identify laboratories performing flow cytometry and discuss with them the feasibility of developing a reporting mechanism for patients with CD4 counts of less than 200×10^6 per liter;
- Increase surveillance activities in outpatient settings;
- Work closely with local tuberculosis control programs to ensure reporting of HIV-infected persons with pulmonary tuberculosis; and
- Identify ways to maintain and strengthen security procedures to ensure protection of confidentiality as the number of cases reported increased.

The CDHS staff assisted local health departments in AIDS case reporting as needed.

In November 1992, the CDHS conducted an assessment of AIDS surveillance programs in the 24 local health departments with the largest number of reported AIDS cases, excluding Los Angeles and San Francisco. Based on this evaluation, the CDHS allocated funds from CDC to 10 local health departments for additional active AIDS surveillance personnel to respond to the increased work anticipated from the expanded case definition. San Francisco and Los Angeles counties also received funds directly from the CDC for this purpose. Among the 41 counties in California reporting more than 20 AIDS cases cumulatively by the end of 1994, 23 (56%) reported cases with only one or more of the four new conditions added in 1993 during the first month of implementation; by March 1993, 35 counties (85%) had reported such cases.

By the end of 1991, the San Francisco Department of Public Health had worked in collaboration with community groups to assess the effects of the proposed expanded AIDS case definition on epidemiologic trends, surveillance activities, CD4 count monitoring, fiscal issues, access to care, and psychosocial and emotional effects on the HIV-infected community. The CDHS held a series of three meetings in 1993 on strategies for enhancing AIDS surveillance, including laboratory reporting of low CD4 counts.

Cases of AIDS diagnosed and reported to the CDHS through December 31, 1994, are included in the analyses presented here. Because the expanded case definition applies only to adults and adolescents, pediatric cases were excluded from analysis. Cases were divided into two groups according to the earliest case definition met at the initial AIDS report: 1987 or earlier definition (pre–1993), or one or more of the four new AIDS-defining conditions added in 1993 (1993-added). Cases classified as 1993-added (n = 19,077) fell into one of three categories: reported only with one or more of the four conditions added in 1993 (88%); also reported with a pre–1993 condition diagnosed after the initial case report (10%); and diagnosed and initially reported only with one or more 1993-added conditions, with a subsequent report of a pre–1993 condition that was diagnosed before or at the same time as the 1993-added conditions (2%).

The incidence of AIDS by year of diagnosis was examined statewide and by region and the presumed mode of exposure to HIV, with an adjustment made for delays in case reporting. Reporting delays were defined as the number of months from an AIDS diagnosis to entry into the local or state registry. These delay adjust-

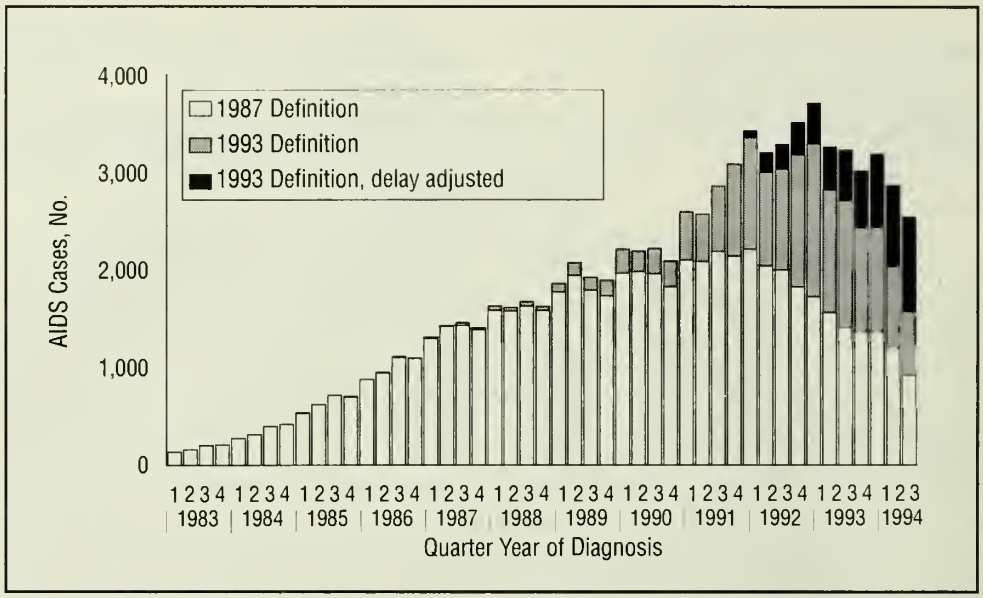

Figure 1.—The graph shows the number of cases of the acquired immunodeficiency syndrome (AIDS) diagnosed in California each quarter of the year, including cases reported to the California Department of Health Services by December 31, 1994. Cases meeting only the 1993 expanded definition of AIDS are represented by the shaded portions of each bar. The upper shaded portion of each bar indicates the total number of diagnosed cases that are expected to be reported by 1997, based on the distribution of delays in case reporting observed before 1993 (adjusted regionally by presumed mode of exposure to the human immunodeficiency virus [HIV] while adjusting for the time of diagnosis). The lower, unshaded portions of each bar represent cases diagnosed with an AIDS-defining disease based on the 1987 case definition in the quarter and the year indicated.

ments were derived for each region by the presumed mode of exposure to HIV while adjusting for the time of diagnosis.[13] These estimates were based on AIDS cases reported before January 1993, using log-linear models and survival analysis techniques for right-truncated data. The delay-adjusted AIDS incidence for the last quarter of 1994 was excluded from analysis because of possible overestimation. To assess changes in timeliness of reporting, we compared median delays in case reporting by quarter-year of report from 1988 to 1994 between cases reported based on pre–1993 AIDS-defining conditions and cases reported based on the four conditions added in the 1993 definition.

To assess shifts in case characteristics due to the expanded criteria, distributions of cases by sex, race or ethnicity, age at diagnosis, region of residence at diagnosis, and mode of exposure to HIV were compared between pre–1993 and 1993-added cases stratified by period of diagnosis (not adjusted for reporting delays). To assess the possible effects on funding for HIV-related services, we calculated the ratio of 1993-added cases to pre–1993 cases among all patients with AIDS presumed living at the end of 1993 (the relative increase due to 1993-added cases). To improve mortality ascertainment, cases were matched with California death certificates through 1993 and with the National Death Index through 1992.

Results

By the end of 1993, a total of 67,170 adult and adolescent cases of AIDS had been reported in California. Of these, 12,371 (18.4%) met only 1993-added criteria when initially reported, with 11,649 (94.2%) reported based on low CD4 counts, 528 (4.3%) based on pulmonary tuberculosis, 172 (1.4%) based on recurrent pneumonia, 17 (0.14%) based on invasive cervical cancer, and 5 (0.04%) based on both recurrent pneumonia and pulmonary tuberculosis. By the end of 1994, the cumulative number of cases reported reached 78,757, with 19,077 (24%) reported as 1993-added cases. Of the 6,706 1993-added cases reported in 1994, 96.4% were reported based on low CD4 counts alone. The 19,629 cases reported in 1993 were 124% more than the 8,780 reported in 1992 and 69% higher than the 11,587 reported in 1994. The number of cases reported based on conditions from the 1987 or earlier definition decreased from 8,780 in 1992 to 7,258 in 1993 and 4,881 in 1994.

Of the 12,371 cases reported in 1993 based on 1993-added AIDS-defining conditions, 60% were diagnosed before 1993; among 1993-added cases reported in 1994, 38% were diagnosed before 1994. The proportion of diagnosed cases reported by December 31, 1994, based on conditions added in 1993, steadily increased. Of the cases diagnosed in 1994 and reported by the end of 1994, 63% were based on 1993-added AIDS-defining conditions.

After adjusting for reporting delays, estimates indicate that the AIDS incidence statewide may have reached a plateau or peaked in 1992 (Figure 1). The AIDS incidence peaked in 1992 in San Francisco for each of the

TABLE 1.—*Characteristics of AIDS Cases Diagnosed Through 1994 and Reported by December 31, 1994, in California, by Year of Diagnosis and Earliest Case Definition Met at Initial Report*

Characteristic	*Pre-1993 Case Definition*				*1993 Case Definition*			
Year(s) of diagnosis	<1992	1992	1993	1994*	<1992	1992	1993	1994*
Cases, No.†	44,042	8,016	4,939	2,681	3,406	4,799	6,690	4,182
County region, %‡								
Los Angeles	36.3	33.7	36.2	35.3	40.2	33.9	29.4	30.1−
San Francisco	24.9	20.0	15.6	14.8−	28.1	25.2	23.4	24.2−
Other Bay Area§	14.2	14.6	14.4	15.1	13.4	17.2	17.6	18.5+
Southern Metro‖	8.9	11.0	12.1	13.7+	7.3	8.5	9.9	10.0+
San Diego	7.5	8.8	8.3	8.2	7.2	7.7	9.4	9.3+
Rest of state	8.3	11.9	13.3	12.8+	3.7	7.4	10.3	7.8+
Exposure mode, %								
Men reporting sex with men (MSM)	78.1	72.1	70.0	68.0−	70.6	70.7	67.9	64.5
MSM and injection-drug user (IDU)	8.9	7.8	6.9	6.6−	9.0	7.9	8.3	8.2
Other IDU	6.2	11.3	11.1	12.2+	11.6	12.3	13.5	14.2+
Heterosexual contact	2.0	3.6	4.7	4.4+	2.7	4.2	4.7	5.2+
Transfusion recipient	2.0	1.2	0.8	1.1−	1.4	0.6	1.1	0.8
Hemophiliac	0.5	0.5	0.5	0.2	0.6	0.6	0.5	0.4
No identified risk	2.4	3.5	6.0	7.6+	4.1	3.7	4.0	6.8+
Sex, %								
Female	3.9	6.2	7.3	7.4+	6.6	7.3	8.4	9.6+
Male	96.1	93.8	92.7	92.6−	93.4	92.7	91.6	90.4−
Race or ethnicity, %¶								
White	70.4	62.0	58.7	56.5−	62.9	60.1	58.2	53.9−
African American	13.0	16.0	16.6	17.4+	18.6	18.7	19.6	21.9+
Latina or Latino	14.5	19.4	21.5	22.3+	16.4	18.8	19.6	21.8+
Asian American	1.6	2.0	2.5	2.8+	1.7	2.0	2.1	1.9
Native American	0.3	0.4	0.3	0.5	0.3	0.4	0.5	0.5
Age at diagnosis, %								
13-19	0.2	0.1	0.2	0.2	0.6	0.2	0.2	0.3
20-29	16.6	14.9	14.7	14.5−	17.6	16.6	16.1	16.6
30-39	45.0	45.1	45.9	45.8	44.1	44.5	45.1	45.2
40-49	25.9	28.0	27.0	29.0+	26.5	27.9	27.3	27.3
≥50	12.3	11.8	12.2	11.1	11.2	10.6	11.4	10.6

AIDS = acquired immunodeficiency syndrome

*+/− indicates that the linear trend in proportion of total cases by year(s) of diagnosis is significantly increasing (+) or decreasing (−), with $P < .01$.

†Figures not adjusted for delays in case reporting. Number of cases diagnosed in the most recent 3 years will increase, and percentage distributions may shift as additional cases are reported that were diagnosed during these years.

‡Includes 28 cases of unknown region.

§Includes Alameda, Contra Costa, Marin, Napa, San Mateo, Santa Clara, Solano, and Sonoma counties.

‖Includes Orange, Riverside, and San Bernardino counties.

¶Includes 160 cases of unknown race or ethnicity.

major HIV exposure groups. The AIDS incidence also peaked or plateaued in 1992 among men reporting sex with men in other regions, with the percentage of changes in incidence from 1992 to 1993 ranging from −13.6% in San Francisco to 1.0% in counties surrounding San Francisco. The incidence also decreased from 1992 to 1993 among men reporting both sex with men and injection-drug use, except in Los Angeles (8.1% increase) and the southern counties of Orange, Riverside, and San Bernardino (27.0% increase). Outside of San Francisco County, the AIDS incidence continued to increase through 1993 for other injection-drug users and for persons with exposure to HIV through heterosexual contact. In all regions but San Diego, the percentage of increases in the incidence from 1992 to 1993 was higher for heterosexual contact cases (from 12.6% in Los Angeles to 30.5% in counties surrounding San Francisco) than for injection-drug users who were women or heterosexual men (from 5.4% in Los Angeles to 33.7% in San Diego).

Characteristics of cases reported based on 1993-added AIDS-defining conditions differed slightly from those reported based on the 1987 (pre–1993) case definition (Table 1). Among cases diagnosed during 1992 to 1994, 1993-added cases were more likely than pre–1993 definition cases to be from San Francisco (24% versus 18%; odds ratio [OR] = 1.48; 95% confidence interval [CI], 1.40 to 1.57) and surrounding counties (18% versus 15%; OR = 1.25; CI, 1.18 to 1.33) and significantly less likely to be from southern metropolitan counties or

the "Rest of state" region. The share of cases from San Francisco and Los Angeles decreased significantly from before 1992 to 1994, from 61.2% to 50.1% among cases reported based on the pre–1993 case definition, and from 68.3% to 54.3% among cases reported based on 1993-added conditions.

Among cases diagnosed between 1992 and 1994, those reported based on 1993-added AIDS-defining conditions were more likely than those reported based on pre–1993 conditions to be injection-drug users who were women or heterosexual (13.3% versus 11.4%; OR = 1.19; CI, 1.11 to 1.28), men reporting sex with men and injection-drug use (8.2% versus 7.3%; OR = 1.13; CI, 1.04 to 1.23) or who had exposure to HIV through heterosexual contact (4.7% versus 4.1%; OR = 1.15; CI, 1.03 to 1.28) and less likely to be men reporting sex with men (67.9% versus 70.8%; OR = 0.87; CI, 0.83 to 0.92). The share of cases attributed to injection-drug use or heterosexual contact increased significantly ($P < .01$) from 8.2% before 1992 to 16.6% in 1994 among cases reported based on pre–1993 conditions and from 14.3% to 19.4% among cases reported based on 1993-added conditions. The expanded definition also increased the proportion of women with AIDS diagnosed in recent years, from 6.7% of pre–1993 cases to 8.4% of 1993-added cases (OR = 1.27; CI, 1.17 to 1.38).

African Americans and Latinos made up an increasing proportion of cases reported based on 1993-added AIDS-defining conditions, accounting for 44% of cases diagnosed in 1994. Of cases diagnosed from 1992 to 1994, 1993-added cases were more likely to be African American than cases reported based on pre–1993 conditions (19.9% versus 16.4%; OR = 1.27; CI, 1.20 to 1.34), whereas the reverse held for whites (57.6% versus 60.0%; OR = 0.91; CI, 0.87 to 0.95). Cases reported based on 1993-added conditions were also more likely than those reported based on pre–1993 conditions to be aged 13 to 19 (0.2% versus 0.1%; OR = 1.76; CI, 1.03 to 3.01) or aged 20 to 29 (16.4% versus 14.8%; OR = 1.13; CI, 1.06 to 1.20) when diagnosed with AIDS during 1992 to 1994 and less likely to be 50 or older (10.9% versus 11.8%; OR = 0.91; CI, 0.85 to 0.98).

The differences between cases reported based on pre–1993 and 1993-added conditions noted earlier were also observed among cases meeting the low CD4 count criterion alone, but these differences were more extreme among those diagnosed with pulmonary tuberculosis, recurrent pneumonia, or invasive cervical cancer. Of the 658 persons diagnosed during 1992 to 1994 based on one or more of these new opportunistic infection and malignancy criteria, 29.2% were heterosexual injection-drug users, 14.3% were women, 39.0% were African American, and 20.4% were 20 to 29 years old at the time AIDS was diagnosed.

Nearly half (46.9%) of the 28,334 cases of patients presumed living at the end of 1993 had been reported based on AIDS-defining conditions added in 1993, representing an 88% increase due to the expanded case definition. Minor differences were observed in the distribution of patients living at the end of 1993 by county according to the earliest case definition met at the initial report. Of the 58 counties in California, 53 had at least one AIDS patient living at the end of 1993. Of these, 19 had increased shares due to the expanded definition, whereas 34 had the same or decreased shares. Among 23 counties with at least 100 patients alive at the end of 1993, the percentage of increase in the number of living patients due to the expanded case definition ranged from 43% to 142%, with a median increase of 86%. The median increase was lower (48%) among the 30 counties reporting fewer than 100 patients living at the end of 1993.

For cases reported during 1988 through 1990, the median delay from the time of the AIDS diagnosis to the time of the report was two months. The median delay increased to three months in 1991 and four months in 1992. During the first quarter of 1993, when the expanded case definition was implemented, the median delay increased to six months for cases reported based on pre–1993 definition criteria and was eight months for cases reported based on criteria added in 1993. The median reporting delay dropped to four months for cases reported during the last quarters of 1994 based on pre–1993 conditions. The median reporting delay dropped steadily from eight months in the first quarter of 1993, however, to two months in each of the last three quarters of 1994 among cases reported based on 1993-added conditions.

Discussion

The number of AIDS cases reported in 1993 in both California and the nation was higher than anticipated.[14] California's share of national AIDS cases dropped slightly from 19.1% in 1992 to 18.1% in 1993 and 17.5% during July 1993 through June 1994.[15,16] Among cases reported in 1993, a higher percentage was reported based on 1993-added conditions in California (63%) than in the nation (54%).[14] Of these cases, a higher percentage was reported based only on severe HIV-related immunosuppression in California (96.4%) compared with the nation (91%).[14]

The number of cases reported based on the low CD4 count criterion alone depends on the number of persons infected with HIV in past years; the length of time from HIV infection to a CD4 count of less than 200 cells $\times 10^6$ per liter, which may be affected by early antiretroviral treatment[17] and age[18]; the number of HIV-infected persons with low CD4 counts who are aware of infection, obtain care, and have CD4 counts enumerated; and the completeness of and delays in reporting of cases to local health departments.[7,14] Dates of diagnosis based on a CD4 T-lymphocyte count below 200×10^6 per liter may vary substantially as a function of the frequency of CD4 count monitoring, response to treatment, testing errors, or transient biologic variability.[19] The large number of cases reported indicates the success of collaborative relationships forged between medical

providers and local, state, and federal AIDS monitoring programs. But has the expanded definition improved our understanding of the epidemiologic characteristics of HIV disease in California?

The primary goal of HIV disease surveillance is to identify targets for and the success of HIV prevention, care, and treatment. Such surveillance data provide population-based evidence to assist health departments and HIV-affected communities in identifying high-priority HIV prevention strategies.[20,21] The expanded case definition allows an earlier identification of trends because AIDS is reportable 12 to 18 months earlier than before and is expected to increase case counts in the long term by about 5%.[10] This has been observed nationwide[14] and in California among injection-drug users, women, and African Americans; the expanded definition appears to have accentuated these previously evolving trends. Similar and even more pronounced findings for women and injection-drug users have been reported in Baltimore, Maryland, and New York City.[22,23] These data alone are not sufficient, however, to identify new targets for primary HIV prevention nor to evaluate such efforts, given the median lag of about ten years between HIV infection and pre–1993 AIDS diagnosis,[24] which has been shortened to a median of 8.5 to 9 years with the expanded definition. Changes in the rate of new HIV infections in a population can be detected by AIDS surveillance only after three to five years, when a sufficient number of persons progressing to AIDS faster are diagnosed and reported.

The shortened lead time with the expanded definition does enhance the identification of targets for HIV care and treatment, resulting in an 88% increase in the number of persons known to require treatment for severe HIV disease in California and indicating the increasing need to ensure access to care among injection-drug users, women, and racial or ethnic minorities. Some counties had relatively larger increases in the number of persons living with AIDS as a result of the expanded AIDS case definition; the amount of local resources available to collect AIDS case data and physicians' and other medical professionals' awareness of case reporting requirements may account for some of these differences. For instance, San Francisco County, with one of the largest increases in the percentage of living cases after the case definition was expanded (122%), launched an aggressive local effort to educate physicians about the change in case definition and has typically had one of the most efficient AIDS surveillance programs, as indicated by shorter delays in case reporting. In contrast, the primarily rural counties with many fewer AIDS cases typically do not have comparable resources for conducting AIDS surveillance.

The expanded definition, on the other hand, has also lessened our ability to monitor the development of opportunistic infections and malignant neoplasms and to evaluate the efficacy of prophylactic treatments. The reported incidence of opportunistic infections will be too low as an increasing number of cases is reported based on the immunologic criterion alone before the development of another AIDS-defining opportunistic infection or cancer. More than half of cases reported in 1994 were reported based solely on the immunologic criterion; this may reflect the possible convenience of reporting cases based on a low CD4 T-lymphocyte count. Subsequent conditions generally are not reported, requiring follow-up of a sample of these patients to accurately ascertain patterns of opportunistic infections and cancers.[25] Of cases initially reported based on AIDS-defining conditions added in 1993, only 10% had a subsequent reported diagnosis of a pre–1993 AIDS-defining condition. In addition, an unknown percentage of cases reported on immunologic grounds may actually have been previously diagnosed with other AIDS-defining diseases that were not reported; this would lead both to a loss of data on opportunistic infections and cancers and to an overestimation of the effect of the 1993 case definition change. At least 2% of the cases reported based only on 1993-added AIDS-defining conditions should have been reported earlier based on the 1987 case definition.

The expanded case definition may have had other influences on the interpretation and use of the data, such as completeness, timeliness, accuracy, and extent of migration. While delays in case reporting initially increased when the expanded definition was implemented, reporting timeliness may now be at levels similar to before the change. The drop in median reporting delay among cases reported based on one or more of the four AIDS-defining conditions added in 1993 probably reflects the initial reporting of previously diagnosed cases. Among cases initially reported based on AIDS-defining diseases from the 1987 definition, extra efforts to implement the expanded definition may have resulted in the more complete identification and reporting of cases diagnosed before 1993, resulting in higher median delays for cases reported in 1993, especially during the first quarters of the year; an increased workload during the beginning of 1993 may account for the longer delays observed later in 1993. The longer delays among cases reported based on pre–1993 AIDS-defining diseases compared with those reported based on conditions added in 1993 may be due to more efficient mechanisms for identifying and reporting cases with CD4 counts of less than 200×10^6 per liter, or may be an artifact because cases with a longer time between diagnosis and reporting are more likely to have developed a pre–1993 AIDS-defining disease before the case is reported. The increase in median reporting delays observed here from 1988 through 1992 are similar to evaluations of the entire delay distribution in California[13] and nationally.[26] The full distribution of reporting delays for cases diagnosed since 1993 will not be known for several years, and the possibility of increased underreporting cannot be ruled out.[26]

It is plausible that the completeness of case reporting increased in 1993 because of the increased surveillance resources, publicity about the expanded case definition, and motivation to report the maximum number of cases to maintain the equitable distribution of funds for HIV prevention, care, and treatment that are allocated at

least partially based on AIDS case statistics. This possibility is supported by the higher-than-anticipated number of cases reported in 1993 and the increase in median reporting delay for cases reported based on the 1987 case definition during early 1993. If this is the case, our estimated AIDS incidence in 1993 adjusted for reporting delays would be too high. If reporting completeness declined in 1994, it would have had to decline by 6% to 28% by the end of 1994 for the AIDS incidence to reach levels observed in 1993. The use of laboratory reports of low CD4 cell counts from large laboratories not currently participating in AIDS surveillance would provide valuable information about AIDS reporting completeness.

Our data suggest that the AIDS incidence in California may have peaked or plateaued in 1992, although a definitive conclusion cannot be made without additional years of observation. Previous projections indicated a slight increase in the incidence between 1992 and 1993 using cases reported through May 1, 1990, according to the 1987 case definition.[27] Thus, with the shorter incubation period provided by the expanded case definition, we would expect to detect a peak earlier. Nationally, based on estimates of the AIDS incidence that would have been observed had CD4 counts not been added to the case definition, there was a 3% increase in the incidence from 1992 to 1993, with a 1% decrease among men reporting sex with men.[28] In San Francisco, the AIDS incidence was estimated to peak in 1992, using information about the annual HIV seroconversion rates, number of persons at risk, and time from HIV seroconversion to AIDS.[29] We obtained similar results using reported AIDS cases from San Francisco.[27]

Even if a plateau or peak has been reached, a large number of cases is still expected to be diagnosed, with about 98,000 to 140,000 HIV-infected Californians who had not progressed to severe HIV disease as of January 1, 1994.[1] This pool of mostly asymptomatic HIV-infected persons provides a large potential reservoir for the transmission of new infections, underscoring the need for continual HIV prevention efforts targeted to those at highest risk. In addition, HIV infections occurring now will not be detectable in the AIDS incidence for at least another three to five years. Further, the HIV epidemic in California consists of multiple subepidemics, so that the epidemic may still be growing in certain groups even in areas such as San Francisco[29] or in certain population groups such as men having sex with men. Outside of San Francisco, the AIDS incidence appears to be increasing through 1994 among injection-drug users and persons presumably infected through heterosexual contact. The AIDS incidence among nonwhite men having sex with men has also increased at a higher rate than among white men having sex with men.[20]

Educating the public about the extent of HIV disease is important for supporting necessary prevention and treatment efforts and influencing changes to safer sex and drug-using practices. The expanded definition has allowed a more complete spectrum of HIV disease to be countable and contributes toward thinking of AIDS as the severe, life-threatening end of the HIV disease spectrum. But it has made the presentation of AIDS monitoring data to the public more difficult during the transition from the previous definition.

When the expanded case definition was first proposed, there were concerns regarding the protection of patient confidentiality, an increased need for psychosocial services, eligibility for services, and differential access to care and CD4 count monitoring.[30,31] With nearly 20,000 AIDS cases reported in California during 1993, there have been no reported breaches of patient confidentiality. Presumptive eligibility for Social Security disability benefits and Medi-Cal (California's Medicaid) was not affected by the revised definition because both programs now require a functional assessment of disability.[32] Regarding the need for psychosocial counseling due to acquiring the label "AIDS" among persons with low CD4 counts with few or no symptoms, an informal survey of social workers in a large HIV specialty clinic revealed no adverse effect of the expanded case definition, although patients tended to be more aware of their CD4 counts (N. Nassar, MD, University of California at Davis, oral communication, February 1994). In the clinical setting, the large biologic and testing variability in CD4 counts should be recognized.[19] Patients with HIV, their advocates, and medical professionals are encouraged to actively participate in the case reporting process. Although studies have shown that a small percentage of HIV-infected persons' CD4 T-cell counts remain stable and they stay free of disease for many years,[33] the information on studies examining symptoms and levels of functioning in HIV-infected persons with low CD4 cell counts but without official opportunistic infections for a long time is limited.

To enhance AIDS surveillance in California, efforts are under way to increase the reporting of AIDS cases by medical professionals and to evaluate the benefits of using laboratories performing CD4 counts to more efficiently identify possible AIDS cases for follow-up with physicians. The 1993 expanded case definition of AIDS has improved our ability to monitor HIV disease in California. To adequately target and evaluate primary HIV-prevention efforts, however, behavioral surveys and HIV seroprevalence and seroincidence surveys are still needed. To this end, the CDHS has initiated HIV serosurveys of young gay men and out-of-treatment injection-drug users and made resources available to local health departments to conduct HIV serosurveys in high-risk groups.

REFERENCES

1. California Department of Health Services (CDHS): Estimates of HIV prevalence and AIDS incidence—California, 1994. Calif HIV/AIDS Update 1995; 8:1-5

2. CDHS: Recent trends in reported AIDS cases in California. Calif HIV/AIDS Update 1993; 6:1-5

3. CDHS: The AIDS epidemic in California: An epidemiologic profile of the first 50,000 diagnosed and reported cases. Calif HIV/AIDS Update 1993; 6:55-62

4. Singleton JA, Otten MW, Doebbert G, Kizer KW: Premature mortality related to HIV infection in California 1981-1993. J Acquir Immune Defic Syndr 1992; 5:688-693

5. Centers for Disease Control and Prevention (CDC): Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; 36(suppl 1)

6. CDC: 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41(No. RR-17)

7. Buehler JW, Ward JW: A new definition for AIDS surveillance: Ann Intern Med 1993; 118:390-392

8. Selik RM, Buehler JW, Karon JM, Chamberland ME, Berkelman RL: Impact of the 1987 revision of the case definition of acquired immune deficiency syndrome in the United States. J Acquir Immune Defic Syndr 1990; 3:73-82

9. Payne SF, Rutherford GW, Lemp GF, Clevenger AC: Effect of the revised AIDS case definition on AIDS reporting in San Francisco: Evidence for increased reporting in intravenous drug users. AIDS 1990; 4:335-339

10. CDC: Projections of the number of persons diagnosed with AIDS and the number of immunosuppressed HIV-infected persons, United States, 1992-1994. MMWR 1992; 41(No. RR-18)

11. CDC: Impact of the expanded AIDS surveillance case definition on AIDS case reporting—United States, first quarter, 1993. MMWR 1993; 42:308-310

12. Rutherford GW: Why, When, How to Report Communicable Diseases. Medical Board of California Action Report 1992; 45:24-25

13. Tabnak F: Multivariate Analysis of Reporting Delay Distribution of AIDS Cases in California (PhD Dissertation). Davis, Calif, University of California, 1994

14. CDC: Update: Impact of the expanded AIDS surveillance case definition for adolescents and adults on case reporting—United States, 1993. MMWR 1994; 43:160-170

15. CDC: HIV/AIDS Surveill Rep 1994; 5(No. 4):5

16. CDC: HIV/AIDS Surveill Rep 1994; 6(No. 1):5

17. Collier AC: Early intervention in HIV infection: Where are we? AIDS Res Human Retroviruses 1994; 10:893-899

18. Rosenberg PS, Goedert JJ, Biggar RJ: Effect of age at seroconversion on the natural AIDS incubation distribution—Multicenter Hemophilia Cohort Study and International Registry of Seroconverters. AIDS 1994; 8:803-810

19. Sheppard HW, Ascher MS, Winkelstein W Jr, et al: Use of T lymphocyte subset analysis in the case definition for AIDS. J Acquir Immune Defic Syndr 1993; 6:285-286

20. California Community Planning Working Group: California HIV Prevention Plan. San Francisco, Calif, Harder & Kibbe Research, October 1994

21. Valdisseri RO, Parra W, Conrad G: Principles of HIV Prevention Community Planning. Presented at the 122nd Annual Meeting of the American Public Health Association, Washington, DC, October 1994, Abstract 1123

22. Chaisson RE, Stanton DL, Gallant JE, Rucker S, Bartlett JG, Moore RD: Impact of the 1993 revision of the AIDS case definition on the prevalence of AIDS in a clinical setting. AIDS 1993; 7:857-862

23. Des Jarlais DC, Wenston J, Friedman SR, et al: Implications of the revised surveillance definition: AIDS among New York City drug users. Am J Public Health 1992; 82:1531-1533

24. Alcabes P, Muñoz A, Vlahov D, Friedland GH: Incubation period of human immunodeficiency virus. Epidemiol Rev 1994; 15:303-318

25. Jones JL, Hanson DL, Chu SY, et al: Surveillance of AIDS-defining conditions in the United States. AIDS 1994; 8:1489-1492

26. Bacchetti P: The impact of lengthening AIDS reporting delays and uncertainty about underreporting on incidence trends and projections. J Acquir Immune Defic Syndr 1994; 7:860-865

27. CDHS: California HIV prevalence estimates and AIDS case projections. Calif HIV/AIDS Update 1992; 5:1-6

28. CDC: Update: Trends in AIDS diagnosis and reporting under the expanded surveillance definition for adolescents and adults—United States, 1993. MMWR 1994; 43:826-831

29. Projections of the AIDS Epidemic in San Francisco: 1994-1997. San Francisco Department of Public Health, February 15, 1994

30. The CDC's Case Definition of AIDS: Implications of the Proposed Revisions—Background Paper. Washington, DC, US Congress, Office of Technology Assessment, OTA-BP-H-89, 1992

31. Chang SW, Katz MH, Hernandez SR: The new AIDS case definition—Implications for San Francisco. JAMA 1992; 267:973-975

32. Social Security Administration—Proposed rules. Federal Register 1991; 56:65702-65713

33. Pantaleo G, Menzo S, Vaccarezza M, et al: Studies in subjects with long-term nonprogressive human immunodeficiency virus infection. N Engl J Med 1995; 332:209-216

Articles

Is There a Role for Parenteral Feeding in Clinical Medicine?

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Protein-calorie malnutrition as evidenced by loss of weight or of lean body mass is a commonly seen disorder. Although its cause is clearly multifactorial, objective measures of protein-calorie malnutrition have been repeatedly correlated with poor patient outcomes. Total parenteral nutrition was developed to halt or reverse this disorder, but its ability to improve the short- to intermediate-term outcome in patients with impaired nutrient intake has been highly inconsistent. Factors influencing this variable outcome include the degree of functional impairment in the treatment group, the underlying disease causing the impaired intake, and possibly the amount and composition of nonprotein calories delivered. In particular, considerable evidence points to intravenous soybean oil emulsion as a negative factor in the nutritional support of stressed patients. Taken in combination, current information suggests reserving the use of parenteral feeding for patients meeting objective criteria for protein-calorie malnutrition and making parsimonious use of lipid emulsion, especially in stressed patients.

(Phinney SD, Siepler J, Bach HT: Is there a role for parenteral feeding in clinical medicine? West J Med 1996; 164:130-136)

Over the past 25 years, total parenteral nutrition (TPN) has progressed from an experimental procedure to an accepted mode of clinical therapy at the community level. Despite this progression to clinical acceptance, however, questions remain as to its optimal composition and dosage. More important, there are also questions concerning its actual effectiveness in improving patient outcome for many of the conditions for which it is currently used.

A Brief History of Total Parenteral Nutrition

Originally called hyperalimentation, TPN was developed as a procedure to support patients being treated surgically who lacked adequate nutritional reserves through the stress of an operation and the catabolism during the immediate postoperative course. Early experience with the procedure suggested that it was most beneficial to severely depleted patients if they received the therapy for at least a week before an elective operation. To achieve rapid energy repletion, goals for adults were often set in the range of 40 to 60 kilocalories (kcal) per kg of body weight, and because lipid emulsion was not available in the United States in the early 1970s, TPN provided before this time consisted mostly of a dextrose solution. Physicians learned a number of lessons from this early experience with TPN, including the need to provide trace metals such as zinc and copper. In addition, the high dextrose loads provided often resulted in hepatic steatosis and occasionally hypercapnic respiratory failure in patients with a limited ability to clear carbon dioxide. With the development of the Broviac and Hickman catheters, the administration of prolonged periods of parenteral feeding became possible, and TPN moved into the outpatient setting, allowing survival and sometimes effective functional lives for patients with the short-bowel syndrome. In 1977 isotonic soybean oil emulsion received approval from the Food and Drug Administration and became available as a source of essential fatty acids and of nondextrose energy for parenterally fed patients. In the past decade, additional tools for adult TPN have included special amino acid mixtures—branched-chain or glutamine-enriched—and peripherally inserted central catheters.

Nutritional Assessment

Before the development of TPN, nutritional assessment was more commonly used in the evaluation of nutritionally disadvantaged populations and third world settings than in acute care clinical medicine. When basic tools adapted from epidemiology were used, surprisingly high rates (>25%) of malnutrition were observed in academic hospitals in the United States.[1-3] Because either the screening tools in these studies were not routinely used in acute care medicine or their nutritional implications were not fully recognized, these early reports not only raised concerns about the nutritional status of patients in acute care hospitals, they also provided a rational basis for assessing an individual patient's need for parenteral feeding.[4]

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TABLE 1.—*Practical Bedside Nutritional Assessment*

Measurement	*Assesses*
History	
Dietary	Recent and past weight loss Functional change—work performance, stairs, ambulation Impaired appetite, taste, smell Dentition, eating, swallowing problems Alcohol use or abuse Religious, self-imposed restrictions
Medical	Chronic illness, fever, cancer Endocrine disease—diabetes mellitus, thyroid, adrenal Gastrointestinal dysfunction, malabsorption Cardiac, pulmonary, renal limitations Neurologic, psychiatric conditions
Pharmacologic	Antimetabolites—immunosuppressive, glucocorticoids, cytotoxic Anticonvulsants Laxatives Vitamins, minerals, nutritional supplements Illicit stimulants—cocaine, methamphetamine
Physical examination	Height, weight Lips, mouth, teeth, mucosa Muscle wasting, hand grip Subcutaneous, adipose Skin texture, rash, ulcers, hair character, nails, pigmentation Reflexes

A limitation of both past and current nutritional assessment techniques is that no single test or procedure provides an irrefutable determination of a patient's nutritional state. In response, assessment procedures have been developed using several variables in combination to categorize patients by their degree of nutritional risk. Such proposed methods of evaluation include the prognostic nutritional index[5] and the global nutritional assessment.[6] It has been noted that a knowledgeable physician can make an adequate assessment of risk independent of biochemical indices,[6] although this may vary with the group of patients being assessed and the level of experience of the assessor. The salient point is that a careful nutritional history—change in or restricted dietary intake—recent change in weight, or change in physical function, coupled with a careful physical examination, yields immediate and useful information in assessing the nutritional risk of a patient in a hospital (Table 1). This approach concurs with that of others who advocate clinically meaningful tests to assess the effects of protein-calorie malnutrition on physiologic function.[7] Suggested tests include hand-grip strength for skeletal muscle function and spirometry to assess respiratory muscle strength.

The primary focus of a nutritional assessment in the acute care setting is the presence and severity of protein and energy malnutrition. Using varying combinations of relative weight for height, skinfold thickness, serum secretory protein levels—for example, albumin, transferrin, prealbumin—history of weight loss, presence or absence of edema, and skeletal muscle assessment (Table 2), a diagnosis of marasmus (loss of body energy reserves), kwashiorkor (protein malnutrition in the absence of energy depletion), or a combination of the two (mixed marasmus and kwashiorkor) can be made. The weight-for-height threshold for marasmus is generally set at 80% to 85% of an arbitrary reference value, such as the midrange of medium-frame values from the 1959 Metropolitan Life Insurance Company tables.[8] Kwashiorkor is diagnosed by the presence of edema—in a patient without congestive heart failure or the nephrotic syndrome—or depressed serum levels of secretory proteins (albumin, <30 grams per liter [3.0 grams per dl]; transferrin, <1.80 grams per liter [180 mg per dl]). Both marasmus and kwashiorkor independently predict poor outcomes in inpatient and outpatient groups.[9-11] Mixed marasmus and kwashiorkor, however, the combination of reduced relative weight for height plus reduced secretory protein levels, carries the highest risk for a poor outcome.[1,12]

Despite the primary focus of nutritional assessment techniques on protein and energy status, several other nutrient levels predict patients' outcome in the acute care setting.[13] Because there are more than 40 nutrients known to be required for human well-being, it is inappropriate to attempt assessing all of them in each patient. For example, a patient with alcoholism will probably be deficient in folate and thiamine, but because these are routinely replaced at the start of parenteral feeding, the initial deficiency does not need to be documented. Nonetheless, an imbalance between macronutrients or trace nutrients and an overt deficiency in one or more required nutrients other than gross protein and energy may have substantial adverse nutritional implications for individual patients and for outcome studies. Deficiencies in intracellular minerals such as potassium, phosphorus, or magnesium may be exacerbated by starting anabolic

TABLE 2.—*Quantitative Assessment Measurements*

Test/Measurement	*Moderate Impairment*	*Severe Impairment*
Weight, % of usual	80-90	<80
Weight:height, % of standard	80-90*	<80
Triceps skinfold, % of standard†	40-60	<40
Creatinine-height index, % of standard‡	80-90	<80
Serum albumin, grams/liter (grams/dl)	28-35 (2.8-3.5)§	<28 (<2.8)
Serum transferrin, grams/liter (mg/dl)	1.50-1.80 (150-180)§	<1.50 (<150)
Total lymphocyte count, $\times 10^9$/liter (/mm^3)	1.0-1.5 (1,000-1,500)§	<1.0 (<1,000)
Delayed-hypersensitivity skin test, mm	5-10 for 1or 2‖	none >5

*Midrange of medium-frame values. From the 1959 Metropolitan Life Insurance tables.[8]

†Men: 12.5 mm; women: 16.5 mm.

‡Creatinine-height index = 24-hour unne creatinine level ÷ ideal 24-hour creatinine × 100. Reference ideal values for women and men are 18 and 23 mg/kg of ideal body weight, respectively.

§Values are given in Système !nternational units, with conventional units given in parentheses.

‖Induration for 4 to 7 antigens at 48 hours.

TABLE 3.—*Common Mineral and Vitamin Deficiencies Affecting Total Parenteral Nutrition*

Mineral or Vitamin Deficiency	*Cause*	*Symptom or Effect*
Sodium	Medications, stress, infection, 5% dextrose in water	↑Aldosterone, potassium wasting, Δmental state, seizure
Potassium	Medications, anabolism, magnesium depletion, ICS*	Weakness, dysrhythmia, protein wasting
Phosphorus	Alcohol, diet, anabolism, ICS*	Weakness, cardiopulmonary collapse, coma, hemolysis, protein wasting
Magnesium	Medications, alcohol, anabolism, diet, fat malabsorption, ICS*	Intractable hypokalemia, muscle cramps, dysrhythmia, seizure, hallucination
Zinc	Medications, diet, alcohol, malabsorption, diarrhea, upper GI fistula	Dry skin, alopecia, ↓taste and smell, ↓cell-mediated immunity, ↓protein synthesis, ↓wound healing
Iron	Blood loss, diet	Weakness, anemia
Thiamine	Alcohol, diet, carbohydrate refeeding	ΔMental state, CHF, edema
Folate	Diet, alcohol, medications	Anemia
Vitamin B_{12}	Malabsorption, diet	Weakness, anemia

CHF = congestive heart failure, GI = gastrointestinal, ↑ = increased, ↓ = decreased, Δ = change in

*Intracellular shift (ICS) occurs when feeding repletes muscle glycogen with a concurrent increase in intracellular fluid.

feeding (refeeding syndrome), and if not effectively corrected, their deficiency can impair protein accretion and the function of specific organs.[14-19] Table 3 provides common examples of mineral and vitamin deficiencies seen before or with the initiation of TPN.

Retrospective Studies and Outcome

In 1980 a retrospective study was done of 145 preoperative patients whose nutritional status was investigated by several objective variables, followed by the observation of postoperative complications such as infection, sepsis, and death.[5] Coincidental with this study, 50 of the patients were given preoperative nutritional support on the clinical judgment of the prescribing physician. Based on the nutritional assessment tool developed as part of this investigation—the prognostic nutritional index—patients were subsequently stratified into three groups based on their degree of nutritional risk. Total parenteral nutrition was provided to nearly equal proportions of all three groups, but significant improvement in outcome was seen in only the most severely malnourished patients to whom this was given. In another study, parenteral feeding was selectively used to replete severely malnourished cancer patients whose clinical status was judged too unstable to allow aggressive intervention for their primary disease.[20] Following nutritional repletion, a sizable proportion of these patients were subsequently able to tolerate the indicated therapeutic intervention. Although there was no control group in this study, the results appeared to indicate that parenteral feeding could successfully replete severely malnourished patients and allow more effective treatment of their underlying diseases.

Prospective Studies Assessing Outcome

Although many prospective studies have assessed the value of TPN in one or more disease states (Table 4),[21-29] many of them included patients who were neither objectively malnourished at the start of therapy nor expected to become malnourished in the normal course of treatment of their disease. Because it is anticipated that TPN would be of benefit only in a patient at high risk for malnutrition, low-risk patients would be unlikely to show benefits but would be at risk of possible side effects resulting from the therapy.

Despite these concerns, several studies deserve comment. In one prospective randomized trial, TPN was provided preoperatively for seven days compared with a normal oral diet as tolerated in preoperative patients with gastrointestinal cancer.[21] The TPN used in that study consisted of 35 kcal per kg of reference body weight as dextrose, a 1.5-gram-per-kg amino acid dose, and no lipids. The incidence of postoperative complications such as wound dehiscence and infections was decreased in the group receiving TPN compared with the control group. Although these patients were not specifically selected for the degree of malnutrition, as a group they had substantially depressed nutrition-related variables as a result of their gastrointestinal cancers.

In a second study, well-nourished bone marrow transplant recipients were randomly assigned to receive or not receive TPN for 35 days of therapy.[26] The rationale for TPN use in this group was the high likelihood of malnutrition developing before the resumption of adequate oral intake. This study showed no notable effect on hospital duration, frequency of infection, or short-term survival. Interestingly, despite the fact that the patients had no circulating granulocytes for at least 25 days following cytoreductive therapy, there was no greater incidence of catheter sepsis or requirement for antibiotics in the patients given TPN. Although there was no apparent benefit of TPN use in the short term, with long-term follow-up, improved survival was noted beginning 100 days after discharge in the group given TPN compared with those who did not receive it during the bone marrow transplantation. This greater survival was the result of a reduced frequency of recurrence of the primary disease, suggesting that TPN given early in the bone marrow transplantation procedure improved the function of donor lymphocytes in sterilizing residual tumor in the host.

A third study involved prospective randomization to therapy that included TPN.[23] The investigators used a combination of parenteral and enteral feeding in patients with obstructive jaundice during preoperative biliary drainage. Patients were randomly assigned either to an

TABLE 4.—*Summary of Studies Assessing Outcome of the Use of Total Parenteral Nutrition (TPN)*

Author, Yr	*Indication or Condition*	*Study Design*	*Results*	*Comment*
Copeland et al, 1979[20]	Malnourished cancer patients unable to tolerate an operation	Retrospective; TPN provided to all patients	Some patients who received TPN were able to have an operation	No control
Mullen et al, 1980[5]	Surgical therapy	Retrospective; patients classified by nutritional status	Patients with severe malnutrition benefited by TPN	No lipid provided
Müller et al, 1982[21]	Surgical therapy, GI cancer	Prospective; TPN versus no TPN	Mortality lower in TPN group	TPN group received no lipid calories
Askanzai et al, 1986[22]	Radical cystectomy	Prospective; TPN versus no TPN	Length of stay in hospital less in TPN group	Outcome analysis retrospective; randomization scheme questionable
Foschi et al, 1986[23]	Obstructive jaundice with biliary drainage	Prospective; enteral nutrition (EN) and TPN versus control	Mortality and complications lower in EN/TPN group	Control group received diet as tolerated and IV fluids
Müller et al, 1986[24]	Surgical therapy, GI cancer	Prospective; TPN versus no TPN	No difference, TPN versus no TPN	Continuation of 1982 study; TPN group now receiving 50% lipid calories
Detsky et al, 1987[25]	Controlled studies of perioperative TPN	Meta-analysis, TPN versus no TPN studies	Fails to show that TPN has any benefit in unselected patietns	Many studies cited had important design flaws to include patients without malnutrition
Weisdorf et al, 1987[26]	Bone marrow transplantation	Prospective; TPN versus no TPN	Fails to show any in-hospital outcome benefit	Long-term survival better in TPN group
VA Cooperative Study Group, 1991[27]	Surgical therapy	Prospective; perioperative TPN versus no TPN	Fewer complications in TPN group only in moderate to severe malnutrition	Overall: more infectious complications in TPN group; all TPN patients received 500 lipid calories
Brennan et al, 1994[28]	Pancreatic resection	Prospective, TPN versus no TPN	No outcome differences; TPN group had more infections	TPN group received 30% lipid calories
Fan et al, 1994[29]	Hepatectomy	Prospective, TPN versus no TPN	TPN group had fewer complications; mortality and length of stay not different	Lipid source was an IV MCT emulsion

GI = gastrointestinal, IV = intravenous, MCT = medium-chain triglycerides

intervention group given enteral and parenteral nutrition as necessary to achieve anabolic protein and energy goals or to a control group given standard therapy consisting of oral intake as tolerated. The preoperative period of biliary drainage lasted an average of 20 days, and the group receiving TPN as part of their mandated feeding showed a substantial reduction in the overall incidence of complications, including infection and death.

In other prospective studies of TPN, two common flaws have caused many of them to be of little value in assessing its role in patients admitted to a hospital. The first is error in the study design or conduct, resulting in the potential of causing more harm than benefit. An example would be a study that provided TPN in combination with aggressive chemotherapy for non-Hodgkin's lymphoma in which the catheter sepsis rate over one month's duration of therapy was 15%.[30] This catheter sepsis rate is five times the accepted catheter sepsis rate for patients with equivalent severity of disease,[31] and thus it negates any interpretive value to be derived from this study. A second error would be the use of a TPN formulation with a composition unlikely to yield notable benefit. This might occur when a profoundly hypercaloric regimen—more than 40 kcal per kg per day in an adult—is given to a patient with kwashiorkor, or the use of a "standard formula" in which patients' specific macronutrient and micronutrient requirements are not individually tailored.

Among studies showing either no beneficial effect or an adverse outcome with TPN, certainly the most interesting was one published in 1986.[24] This study revealed a third limb to the study published by the same group in 1982.[21] The third limb involved similar energy and nitrogen goals relative to their original no-lipid-TPN group, but 50% of the energy was provided as soybean oil lipid emulsion. The authors report that this limb of the study was discontinued prematurely due to excess mortality over the group receiving lipid-free TPN, although the overall mortality in the lipid group was similar to that of the non-TPN controls. The increase in mortality over this group was due to infection. What was not explained was why this group's results were not published with the

initial report four years earlier.[21]

The largest prospective study of TPN use published to date is the Veterans Affairs perioperative TPN trial.[27] This study assessed more than 3,000 patients; excluded many, including those with extremes of underweight, hypoalbuminemia, and comorbid conditions; and eventually randomly assigned 395 patients to preoperative TPN for seven days versus whatever oral intake was tolerated. The study revealed no differences in overall morbidity and mortality in the group receiving TPN compared with those on oral intake, but there was an increased incidence of noncatheter sepsis in the TPN-receiving group. The TPN in this study included a fixed dosage of 500 kcal per day provided as lipid emulsion, and, in addition, the TPN-receiving group took 850 kcal per day orally compared with the 1,300 kcal per day consumed by the non–TPN-receiving group. An important note in interpreting this study's results is that, due to their exclusions in initial patient screening, the mean weight and serum albumin level of the subjects receiving TPN were 89% of the reference weight for height and 31 grams per liter, respectively. These mean values are above the generally accepted thresholds for substantial nutritional risk—that is, a serum albumin level <30 grams per liter and weight <85% of reference. Thus, compared with other studies showing a beneficial effect of preoperative TPN use on the outcome, this group was considerably better nourished overall.

A third prospective randomized trial with an adverse outcome was one in which preoperative TPN was provided prospectively to patients undergoing pancreatic resection.[28] This group of patients is known to have a high risk for malnutrition developing in the course of perioperative management; nonetheless, this study showed no net improvement in the group receiving TPN compared with the non–TPN-receiving controls, and the TPN recipients had a higher risk of infectious complications. Again, in this study, the TPN contained a fixed dose of soybean oil emulsion.

Possible Confounding Factors in Interpreting Outcome Studies Using Total Parenteral Nutrition

The highly variable response to well-designed studies involving perioperative TPN use clearly makes a uniform statement of its efficacy questionable. The Veterans Affairs study can be criticized for its excluding severely malnourished patients and, in so doing, excluding that subgroup of patients most likely to benefit from this therapy.[27] This study also underscores the value of objective assessments of nutritional status as a tool for stratifying patients' risk. Other variables include the level of energy provision, as calorie overfeeding in studies of animals increases animal mortality when they are challenged by infection.[32] Another poorly understood variable is the provision of iron during nutritional resuscitation, as the body's defense against allowing bacterial access to iron is transferrin, levels of which are depressed with protein malnutrition.[33] In a prospective randomized study with or without oral iron during nutritional repletion, infectious risk was increased threefold in those subjects receiving oral iron.[34] Although iron is not always provided in TPN, it is routinely included in enteral formulations; an argument can be made for its temporary omission by either route in the early phase of treatment of acutely stressed or severely malnourished patients.

A clue to a previously unsuspected variable in the intersection between nutritional support and infection was found in a randomized prospective trial of three enteral feeding regimens in burn patients.[35] An increased incidence of infectious complications and death was reported in a group of patients receiving a commercially available enteral formula relatively high in fat. Because uniform levels of protein, minerals, and vitamins were provided by all three formulas, this raises the suspicion that the high polyunsaturated-fat content of the formula in question may play a causative role. Numerous studies of animals have shown varying degrees of immunosuppression when polyunsaturated-fat intake is increased, particularly when it is of the ω6 class of polyunsaturated fats.[36] In light of these studies, this raises the concern that recent well-designed studies of TPN may have resulted in an increased incidence of infections and no objective benefit as a result of including soybean oil emulsion (high in ω6 fatty acids) as a major energy source.

The primary rationale for including soybean emulsion in TPN is to provide essential fatty acids. The human requirement for ω6 fatty acids, specifically linoleate, is met by 1% and 4% of daily energy intake as linoleate.[37] This level of linoleic acid contribution as calories can be met by providing between 2% and 8% of energy as soybean oil emulsion. Over the past ten years, however, it has become customary to provide 20% to 50% of energy as lipid emulsion to reduce the dextrose load and avoid hyperglycemia, particularly in stressed or insulin-resistant patients. This practice, based on a presumption of benefit, may have then contributed to the negative outcomes in otherwise well-designed studies.

New information on the provision of essential fatty acids in parenterally fed patients offers the possibility of avoiding the use of intravenous lipids in many patients, particularly those who are acutely stressed. In 1979 it was shown that in patients given TPN on a daily cyclic regimen in which glucose infusion was withheld for at least eight hours, essential fatty acid deficiency was avoided by using the normally copious endogenous reserves of linoleic acid in adipose tissue.[38] Because adipose tissue in North Americans contains roughly 15% linoleate, it is a rich source of this essential fatty acid. Recently, the use of mildly hypocaloric TPN regimens was studied in normal-weight to obese patients for durations of as long as three months, and no biochemical evidence of essential fatty acid deficiency was found.[39] Although the diagnostic criteria for essential fatty acid adequacy have recently been questioned,[40] the previously mentioned study showed no increase in Mead acid,[39]

the triene marker of essential fatty acid deficiency.[41] Although hypocaloric TPN carries a theoretical metabolic risk of allowing suboptimal nitrogen conservation, a number of studies have shown effective nitrogen sparing with hypocaloric TPN in normal-weight and obese patients with mild to moderate stress.[39,42-44]

Taken in combination, these studies indicate that TPN can be provided with little or no intravenous lipid emulsion in many patients. This can be safely achieved by either a cyclic regimen providing maintenance or anabolic energy or by a continuous hypocaloric regimen. Both methods make effective use of the patients' copious reserves of adipose linoleic acid. For patients with severe marasmus who do not have substantial endogenous lipid stores, the dose of lipid emulsion needed to meet basic essential fatty acid needs is at or below 10% of total energy requirement.

Costs of Total Parenteral Nutrition

The actual cost to formulate and administer adult TPN for one day varies between $100 and $300.[28] When provided for otherwise fatal conditions such as the short-bowel syndrome, properly formulated TPN prolongs life by one day for each day it is administered. At yearly costs of $40,000 to $100,000, outpatient TPN is comparable to the cost of long-term dialysis (>$30,000 yearly, including erythropoietin therapy; T. Depner, MD, oral communication, November 1995) and is considerably less expensive than primary prevention therapy for atherosclerosis by cholesterol-lowering drugs.[45] Based on the results of early studies showing that the use of TPN without lipid reduced the incidence of postoperative infections, the cost-benefit ratio of perioperative TPN use was favorable relative to the otherwise necessary costs of a prolonged hospital stay and antibiotic therapy.[46] As current TPN practices do not demonstrate the previously observed reduced incidences of infection, however, there is no benefit to balance against the cost except in the most severely malnourished patients. For conditions in which surgical intervention has variable success such as Crohn's disease with obstruction or nonmalignant enterocutaneous fistula, the use of TPN to avoid surgical therapy can be cost-effective, especially if administered at home. The one caveat in these conditions is that they are commonly accompanied by pronounced deficiencies in magnesium, phosphorus, and zinc due to malabsorption, and the healing process is slowed or prevented unless these minerals are effectively replaced.

Conclusion

Total parenteral nutrition is a complex prescription requiring patient-specific formulation to prevent metabolic complications that can subvert its benefits. Acutely stressed and severely malnourished patients are a special challenge to clinicians. Although these patients are most likely to benefit from parenteral feeding, they are also the most labile, and thus the optimal TPN formulation should be patient-specific and frequently reformulated in response to patients' changing clinical states. The use of TPN has shown little benefit in patients with little or no evidence of malnutrition in whom brief (<7 to 10 days) periods of starvation are anticipated.

Considerable evidence points to an adverse role for soybean oil emulsion in outcome studies of adult patients who are stressed or not severely malnourished. Studies involving the use of little or no lipid have demonstrated positive benefits of TPN use, whereas those providing more than 20% of energy as lipid emulsion have generally yielded no benefit. The practical implications of this perspective are that the use of TPN should be reserved for patients who have objective signs of moderate to severe malnutrition or those with a high likelihood of becoming malnourished as a result of their current illness or therapy (or both).

For adult patients at or above normal body weight who are given TPN, lipid can be omitted from the TPN prescription for at least a month if the patients' intake from all sources provides energy at or below 25 kcal per kg of reference (ideal) weight. Alternatively, anabolic TPN without lipid (30 kcal per kg of reference weight) can be infused over a 16-hour cycle with an 8-hour period without glucose infusion. For the rest of patients requiring anabolic energy by continuous infusion, intravenous lipid emulsion may be included for as much as 10% of total energy.

Future additions to our therapeutic armamentarium will include lipid emulsions providing a mix of medium-chain fatty acids plus a modicum of long-chain polyunsaturated fats, or lipid emulsions formulated from highly monounsaturated oils with a minor polyunsaturated content. These new products may obviate the restrictions that this review implies are necessary for current soybean oil emulsions rich in polyunsaturated fatty acids. In addition, well-designed prospective clinical studies are needed to validate the therapeutic benefit of low-lipid or nonlipid TPN under the presumptive guidelines outlined above.

REFERENCES

1. Butterworth CW, Blackburn GL: Hospital malnutrition and how to assess the nutritional status of a patient. Nutr Today 1975; 10:10-18

2. Bistrian BR, Blackburn GL, Hallowell E, Heddle R: Protein status of general surgical patients. JAMA 1974; 230:858-860

3. Bistrian BR, Blackburn GL, Vitale J, Cochran D, Naylor J: Prevalence of malnutrition in general medical patients. JAMA 1976; 235:1567-1570

4. Blackburn GL, Bistrian BR, Maini B, Schlamm HT, Smith MF: Nutritional and metabolic assessment of the hospitalized patient. JPEN J Parenter Enteral Nutr 1977; 1:11-22

5. Mullen JL, Buzby GP, Matthews DC, Smale BF, Rosato EF: Reduction of operative morbidity and mortality by combined preoperative and postoperative nutritional support. Ann Surg 1980; 192:604-613

6. Baker JP, Detsky AS, Wesson DE, et al: Nutritional assessment: A comparison of clinical judgement and objective measurements. N Engl J Med 1982; 306:969-972

7. Windsor JA, Hill GL: Weight loss with physiologic impairment—A basic indication of surgical risk. Ann Surg 1988; 207:290-296

8. Build and Blood Pressure Study, Vols I and II. Chicago, Ill, Society of Actuaries, 1959

9. Studley HO: Percentage of weight loss—A basic indicator of surgical risk in patients with chronic peptic ulcer. JAMA 1936; 106:458-460

10. Cannon PR, Wissler RW, Woolridge RL, Beneditt EP: The relationship of protein deficiency to surgical infection. Ann Surg 1944; 120:514-525

11. Corti MC, Guralnick JM, Salive ME, Sorkin JD: Serum albumin and physical disability as predictors of mortality in older persons. JAMA 1994; 272:1036-1042

12. Harvey KB, Moldawer LL, Bistrian BR, Blackburn GL: Biological measures for the formulation of a hospital prognostic index. Am J Clin Nutr 1981; 34:2013-2022

13. Weinsier RL, Hunker EM, Krumdieck CL, Butterworth CE Jr: Hospital malnutrition—A prospective evaluation of general medical patients during the course of hospitalization. Am J Clin Nutr 1979; 32:418-426

14. Rudman D, Millikan WJ, Richardson TJ, Bixler TJ, Stackhouse WJ, McGarrity WC: Elemental balances during intravenous hyperalimentation of underweight adult subjects. J Clin Invest 1975; 55:94-104

15. Jacob HS, Amsden P: Acute hemolytic anemia with rigid red cells in hypophosphatemia. N Engl J Med 1971; 285:1446-1450

16. O'Connor LR, Wheeler WS, Bethune JE: Effect of hypophosphatemia on myocardial performance in man. N Engl J Med 1977; 297:901-903

17. Auhier M, Murciano D, Lecocguic Y, et al: Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med 1985; 313:420-424

18. Flink EB, Brick JE, Shane SR: Alterations of long chain free fatty acid and magnesium concentrations in acute myocardial infarction. Arch Intern Med 1981; 141:441-443

19. England MR, Gordon G, Salem M, Chernow B: Magnesium administration and dysrhythmias after cardiac surgery. JAMA 1992; 268:2395-2402

20. Copeland EM, Daly JM, Old DM, Dudrick SJ: Nutrition, cancer, and intravenous hyperalimentation. Cancer 1979; 43:2108-2116

21. Müller JM, Brenner U, Dienst C, Pilchmaier H: Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet 1982; 1:69-71

22. Askanazi J, Hensle TW, Starker PM, et al: Effect of immediate postoperative nutritional support on length of hospitalization. Ann Surg 1986; 203:236-239

23. Foschi D, Cavagna G, Callioni F, Morandi E, Rovati V: Hyperalimentation of jaundiced patients on percutaneous transhepatic biliary drainage. Br J Surg 1986; 73:716-719

24. Müller JM, Keller HW, Brenner U, Walter M, Holzmuller W: Indications and effects of preoperative parenteral nutrition. World J Surg 1986; 10:53-63

25. Detsky AS, Baker JP, O'Rourke K, Goel V: Perioperative parenteral nutrition: A meta-analysis. Ann Intern Med 1987; 107:195-203

26. Weisdorf SA, Lysne J, Wind D, et al: Positive effect of prophylactic total parenteral nutrition on long-term outcome of bone marrow transplantation. Transplantation 1987; 43:833-838

27. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group: Perioperative total parenteral nutrition in surgical patients. N Engl J Med 1991; 325:525-532

28. Brennan MF, Pisters PWT, Posner M, Quesada O, Shike M: A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Ann Surg 1994; 220:436-444

29. Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J: Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 1994; 331:1547-1552

30. Popp MB, Fisher RI, Wesley R, Aamodt R, Brennan MF: A prospective randomized study of adjuvant parenteral nutrition in the treatment of advanced diffuse lymphoma: Influence on survival. Surgery 1981; 90:195-203

31. Ryan JA Jr, Abel RM, Abbott WM, et al: Catheter complications in total parenteral nutrition—A prospective study of 200 consecutive patients. N Engl J Med 1974; 290:757-761

32. Peck MD, Babcock GF, Alexander JW: The role of protein and calorie restriction in outcome from Salmonella infection in mice. JPEN J Parenter Enteral Nutr 1992; 16:561-565

33. Kluger MJ, Rothenherg BA: Fever and reduced iron: Their interaction as a host defense response to bacterial infection. Science 1979; 203:374-376

34. Murray MJ, Murray AB, Murray MB, Murray CJ: The adverse effect of iron repletion on the course of certain infections. Br Med J 1978; 2:1113-1115

35. Gottschlich MM, Jenkins M, Warden GD, et al: Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. JPEN J Parenter Enteral Nutr 1990; 14:225-236

36. Kinsella JE, Lokesh B, Broughton S, Whelan J: Dietary polyunsaturated fatty acids and eicosanoids: Potential effects on the modulation of inflammatory and immune cells. J Nutr 1990; 6:24-44

37. Riella MC, Broviac JW, Wells M, Schribner BH: Essential fatty acid deficiency in human adults during total parenteral nutrition. Ann Intern Med 1975; 83:786-789

38. Mascioli EA, Smith MF, Trerice MS, Meng HC, Blackburn GL: Effect of total parenteral nutrition with cycling on essential fatty acid deficiency. JPEN J Parenter Enteral Nutr 1979; 3:171-174

39. Parness HL, Mascioli EA, LaCivita CL, et al: Parenteral nutrition in overweight patients: Are intravenous lipids necessary to prevent essential fatty acid deficiency? J Nutr Biochem 1994; 5:243-247

40. Siguel EN, Lerman RH: Altered fatty acid metabolism in patients with angiographically documented coronary artery disease. Metabolism 1994; 43:982-993

41. Holman RT: Essential Fatty Acid Deficiency—Progress in the Chemistry of Fat and Other Lipids. Elmsford, NY, Pergamon Press, 1968, pp 279-348

42. Greenberg GR, Jeejeebhoy KN: Intravenous protein sparing therapy with gastrointestinal disease. JPEN J Parenter Enteral Nutr 1979; 3:427-432

43. Dickerson RN, Rosato EF, Mullen JL: Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr 1986; 44:747-755

44. Burge JC, Goon A, Choban PS, Flancbaum L: Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: A prospective, double-blind randomized trial. JPEN J Parenter Enteral Nutr 1994; 18:203-207

45. Oster G, Epstein AM: Cost-effectiveness of antihyperlipemic therapy in the prevention of coronary heart disease. JAMA 1987; 258:2381-2387

46. Twomey P, Patching S: Cost-effectiveness of nutritional support. JPEN J Parenter Enteral Nutr 1985; 9:3-10

Articles

Conflicts Between Managed Care Organizations and Emergency Departments in California

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To control costs, managed care organizations have begun to restrict the use of hospital emergency departments by their enrollees. They are doing this by educating enrollees, providing better access to 24-hour urgent care, denying preauthorizations for care for some patients who do present to emergency departments, and retrospectively denying payment for certain patients who use emergency services. Changing traditional use of emergency departments has resulted in conflicts between managed care organizations and these departments. Because federal law mandates access to emergency care for all persons, disagreements occur over the precise definition of an emergency medical condition. In addition, conflicts occur over the scope and payment for the medical screening examination required by federal law of persons presenting to an emergency department. Finally, issues arise related to the safety of patients who present to emergency departments and request care but are denied care because the managed care organization does not authorize the visit. Recent legislation in California has attempted to reconcile differences between managed care practices and federal and state laws; however, areas of continued conflict need to be resolved to prevent possible adverse consequences for patients actually needing emergency care.

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The conflict between managed care organizations (MCOs) and emergency medical services evolves from the fundamental differences in mission and philosophy that characterize the two systems. Emergency medicine focuses on episodic crises, necessitating open access and standby readiness, whereas managed care focuses on primary and preventive health care and the planned use of available resources. In certain areas of the country, including California, managed care and cost containment are having a substantial effect on the delivery of health care in emergency departments. The transition from the old fee-for-service reimbursement structure has been difficult to incorporate into emergency medical services.[1-3] Managed care organizations are potentially at odds with public safety and federal laws governing emergency care.[4]

Federal Law

Hospital emergency departments have an ethical and legal obligation to examine all patients who present for care and to provide stabilizing treatment of patients with emergency medical conditions. Under federal emergency care access and transfer statutes, known as the Emergency Medical Treatment and Active Labor Act (EMTALA) and more commonly by the acronym COBRA [Consolidated Omnibus Budget Reconciliation Act], all patients who present to a hospital emergency department are entitled to a medical screening examination by a qualified medical professional, to determine the presence or absence of an emergency medical condition.[5,6] This examination must be done regardless of a patient's ability to pay or technical competence to provide consent. Managed care organization gatekeepers are frequently unable to assess the need for emergency medical care over the telephone and must defer their clinical control to those in attendance. Ultimately, any discharge or transfer from an emergency department is regulated by COBRA. Violations may result in severe fines, termination of a hospital or a physician's Medicare affiliation, and additional civil liability.

Some confusion arises from the use of the term "screening examination," which implies to some a cursory evaluation. Under COBRA, however, a medical screening examination must be sufficient to rule out the need for emergency medical care and may range from a brief examination to a detailed examination involving all of the laboratory, x-ray, and consultative resources available within a hospital's range of services.[6] Many hospitals consider anyone needing detailed evaluation or ancillary services in an emergency department to have an emergency until proved otherwise. Further, under COBRA, hospitals with specialized service capabilities, such as a burn or trauma center, have a duty to receive

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ABBREVIATIONS USED IN TEXT

COBRA = Consolidated Omnibus Budget Reconciliation Act
EMS = Emergency Medical Services
MCO = managed care organization

patients in transfer from those that lack such capabilities, when such care is needed for stabilization.[5]

Definition of Emergency Care and Services

A major factor in the debate regarding the appropriate use and payment for an emergency has been the disagreement among agencies on the definition of these services and the conditions to which they apply. Under COBRA, a medical emergency is a condition that poses an immediate threat to a patient's survival or may result in permanent loss of function of an organ or body part or severe pain.[6] California law extends the definition to include any condition that may result in a disability.[7] Managed care organizations use life-threatening definitions, with the expectation that plan members would avoid seeking out-of-plan emergency care unless they know that the delay in transit to the MCO facility would result in dire consequences. On the contrary, emergency care providers tend to emphasize definitions that recognize high-risk or occult conditions or those that result in moderate pain incorporating a patient's perception of need for the evaluation of acute symptoms.[8] In our experience, most patients who come to emergency departments are genuinely concerned for their safety and think that their condition might be a serious threat to their well-being.

Cost Shifting and Financing of Emergency Services

Over the past decade, emergency departments have become a focus of excessive hospital cost shifting. Many have functioned as the primary source of health care for indigents due to the absence of other sources of care in their communities.[9-12] In addition, with the introduction of diagnosis-related groups in the 1980s, hospitals have had more difficulty shifting costs for inpatient services, placing further emphasis on outpatient cost shifting to maintain profitability. The resultant acceleration of outpatient costs has concerned MCOs, motivating them to control access by requiring prior authorization.

Emergency departments have also become increasingly expensive to operate. They provide numerous essential community services, yet they have largely been taken for granted as community resources. Federal law has led to a higher standard of emergency care, but it has also led to increased costs in the total provision of care to all regardless of patients' financial status. Hospitals face the increasingly difficult challenge of providing resources and specialty on-call coverage commensurate with their COBRA responsibility. In the past, those specialists who have volunteered their on-call services have received relatively low fee-for-service compensation from payers because of the largely indigent patient mix in emergency departments. In managed care situations, however, emergency department patients represent an obligation to provide out-of-contract services with no guarantee of reimbursement. Under federal law, hospitals with emergency departments are required to maintain specialty consultation coverage if it is otherwise available within a hospital's range of services.[6] Because this is a hospital's responsibility, it has shifted much of the cost of providing specialty coverage from a voluntary to a contractual basis at the hospital's expense.[13] Some MCOs have taken advantage of this situation: their enrollees will have complete care even if they decide not to reimburse the physicians and hospital.

Many MCOs using various methods of gatekeeping have successfully discouraged inappropriate use of an emergency department. Recently, several states have applied these same strategies to Medicare and Medicaid programs. Some emergency departments in heavily managed markets have experienced substantial census reductions.[14] We see the following trends developing:

- Emergency departments will be under continuing pressure to contain costs and create efficient lines of service, accentuating the current trend for the development of observation units and nonemergent fast-track services;
- There will be a continuing trend toward emergency department capitation; and
- There will be an acceleration of COBRA enforcement activity, as hospitals with marginal economic viability experience further difficulty in maintaining full services.

The influence of managed care is also extending to the prehospital care area, where costs have likewise accelerated in recent years. Paramedics are being trained to provide out-of-hospital, first-aid care to minimize the need for transport to an emergency department. Dedicated telephone numbers, such as 311 or 511, are being developed in some areas of the country to bypass the 911 Emergency Medical Services (EMS) system.[15] Many large hospital systems own or contract for ambulance services for transporting their patients, and it is relatively easy to expand these services into prehospital care for their MCO patients ("EMS About to Undergo Radical Changes," *EMS Insider* 1994; 21:1-4). Under Health Care Financing Administration regulations, ambulance services—when "owned" by the hospitals—are subject to COBRA regulations.[4] The 911 bypass phenomenon is relatively new, however, and has thus far been unregulated. Consequently, whereas market reform of the EMS system offers the potential for major improvements in service efficiency, this phenomenon is certain to raise additional concerns, including threats to the integrity of regional EMS and trauma systems.

Taking Advantage of Emergency Departments' Requirement to Provide Care

Many MCOs have pursued policies of challenging and refusing to reimburse hospitals and physicians for the

provision of emergency care, despite the hospitals' mandate to provide this care and despite the fact that this service is a required covered benefit.[14,16,17] In northern California, this is accomplished by requiring emergency department registration personnel to place a telephone call for authorization to a gatekeeper before service can be provided.[4] In many cases, the gatekeeper is not the patient's primary care physician or an on-call physician. Managed care organizations refer to this process as "treatment authorization," despite the fact that it applies to insurance authorization only. The gatekeeper may then deny authorization on the basis of a patient's chief complaint or on the basis of a preliminary assessment by the triage nurse. The patient is then placed in the position of weighing his or her medical risk versus a personal financial risk and of having to consider going against the advice of a physician to obtain a needed service. The hospital must make sure that patients understand their right to obtain a medical screening examination and must document patients' refusal of further service, despite the difficulty of ensuring that this decision is an informed one.

Using the rationale that the claim can always be reviewed and paid later, if necessary, MCOs have been known to publish policies advocating the routine denial of "treatment authorization," and, in some instances, patients with obvious life-threatening conditions have been denied authorization.[16] Patients in severe pain and those who have had a myocardial infarction, pulmonary emboli, or ectopic pregnancy have been denied initial authorization and told to go to the MCO clinic.[4] In addition, in our experience, MCOs frequently reserve the right to deny a claim based on retrospective review, even when prior authorization was given. Thus, a final diagnosis of dyspepsia could be used as the rationale for refusing to pay for an evaluation for chest pain, despite the fact that the patient required a medical screening examination to rule out ischemic heart disease.

Several states have recently developed managed care and capitated contracting for their Medicaid patients, a trend that has accelerated following the failure of national health care reform efforts in 1994.[18] In these programs, the state contracts with health maintenance organizations or primary care case management organizations for full coverage or outpatient primary care. Several such programs that were created as demonstration programs now involve 36 states and 25% of all Medicaid patients ("Federal Agency Activity Remains High," *ACEP* [American College of Emergency Physicians] *News* 1994; 13:18). Thus far, only Arizona, Utah, and Tennessee have implemented their programs statewide, whereas California, Washington, and other states are planning phased implementation.[19] Although these programs have succeeded in making primary medical care available to beneficiaries, they have also been responsible for major disruptions in the modes of access and financing for needed emergency services.[13] The California and Tennessee programs have been characterized by minimal control at the state level and vast confusion in assigning and educating beneficiaries. Contracting plans have been free to apply the same rationale for denying authorization and reimbursement used by MCOs in general.[13] Gatekeeping responsibilities have been relegated to nonmedical personnel answering remote 800 telephone numbers during partial hours of service.[4] Lacking a detailed knowledge of patients' signs and symptoms and of local medical resources, these gatekeepers are nonetheless empowered to make critical authorization and referral decisions, further imperiling patients and providers. Theoretically, all patients in such programs have an assigned primary care physician; in practice, however, the alternative sources of primary care are often small after-hours clinics with little capability to provide acute care.

To reconcile tensions between emergency medicine and MCOs, California passed legislation effective January 1995. Revisions to section 1317.4 of the Health and Safety Code, commonly referred to as the Bergeson Bill, state that an emergency department should provide initial stabilizing care without first calling the MCO for authorization for patients having a medical emergency.[20] Furthermore, the MCO is required to pay for services but may appeal following a specific procedure.

Emergency Department Self-Gatekeeping as a Partial Solution to the Managed Care Issue

One solution is for emergency departments to develop self-gatekeeping and to refer patients with nonemergent problems out of the emergency department. This has several possible advantages:

- It may be a more cost-effective use of health care dollars,
- It may decrease the number of preauthorization calls between emergency departments and MCOs,
- In return for patients with nonurgent problems being referred out of emergency departments, MCOs may be more accepting of emergency departments that provide care to the remaining patients.

Several factors have, so far, inhibited the development of emergency department self-gatekeeping. First has been the lack of alternative primary care services to which emergency departments may refer patients with minor conditions. Some emergency physicians have considered it unethical to refuse such service to patients who have even minor complaints. Theoretically, Medicaid-managed care programs and other proposals for universal coverage will solve this problem; however, several authors have described a variety of additional barriers to obtaining primary care access, even in settings where these resources have been provided.[21] Finally, there has been the presumption that the risk of a COBRA violation necessitates that physicians do a medical screening examination or a complete evaluation in all cases.[22] This stems from the desire of hospitals and emergency physicians to provide a uniform standard of care beyond COBRA reproach.

Managed care organizations have focused on emergency department use by patients with nonemergent

problems. The actual number of patients who present to an emergency department with nonurgent problems, however, is unknown. Studies by several agencies based on retrospective diagnostic criteria estimate that 40% to 55% of patients seen in emergency departments have nonurgent problems.[19,23] Those based on prospective symptom criteria have estimated this nonurgent visit frequency to be more in the range of 15% to 20%.[24,25]

The concept of referring outpatients after a brief medical screening examination has recently evolved in the specialty of emergency medicine. The initial motivation for referring patients with nonurgent problems out of the emergency department came from overcrowding in these departments.[25] At present, most emergency departments treat everyone, no matter how trivial the problem. This has resulted in strained relations between MCOs that seek to contain costs by managing access and emergency departments that are required by law to provide evaluation and stabilize care. There has been no agreed-on national standard for defining levels of urgency in the presentation of patients to emergency departments.[26] In the absence of published and accepted national standards, many emergency department triage programs are written locally and oriented to the needs of each department. Thus, there is great variation in definition, training, and quality standards between institutions, resulting in considerable disagreement among experts regarding the safety of these programs when used to restrict access.[22,27,28] In our experience, triage nurses are increasingly overburdened with the bureaucracy of managed care, including communicating with gatekeepers, documenting decisions, and explaining risk. The combination of managed care barriers, overcrowding, long waiting times, and high rates of patient elopement has placed ever-greater emphasis on clinical triage as an essential means of ensuring access and safety in emergency departments.

Medical Screening Examination

The term "triage" originated from the classification of casualties of war or other major disasters to determine priority of need and the proper place of treatment. In the emergency department context, clinical triage by nurses is a well-established process used to determine acuity level and prioritize care. Such programs were never intended to serve a legal purpose; however, the triage examination can be expanded to meet the requirement for the medical screening examination under certain circumstances.[22] As to the controversial issue of who does the screening examination, the Health Care Financing Administration has determined that it must be a qualified medical professional, in accordance with the scope of practice limitations dictated by state law. If performed by a nonphysician, the program must be authorized under the hospital's rules and regulations as opposed to sole emergency department policy. The role and scope of responsibility and the qualifications of persons must be delineated. In addition, the examination must be done under standardized procedures.

Initial Medical Screening Examination

- Assess chief symptom: Chronic condition, at risk, or a true emergency?
- Vital signs
- Mental state: Evidence of change?
- General appearance: Does the patient look sick?
- Degree of pain: Does the patient have moderate or severe pain?
- Skin: Evidence of dehydration, poor perfusion?
- Focused physical examination: See non-emergency section for details
- Ability to walk
- Pregnancy: Is the patient near term?

Figure 1.—The medical screening examination (MSE) must be done on all patients who present to an emergency department and request medical care. The purpose of the MSE is to determine if a patient has an emergency medical condition and, if one exists, to assign the patient to the appropriate triage category. No information about payer status, health maintenance organization membership, or insurance shall be asked by the person doing the examination. The results of this examination are recorded on the screening examination form and become a part of the patient's permanent medical record.

We think many emergency departments can expand the examination performed by triage nurses to meet the federal definition of a screening examination. If the case is unclear, a more detailed screening examination should be done by a physician. This represents a reasonable and effective method to ensure timely access and referral to appropriate settings of care. Such a program was initially developed at the University of California, Davis, and has now been in operation for more than six years, with more than 30,000 patients having been referred to off-site care.[22] Their initial screening examination does not include laboratory tests or x-ray films (Figure 1). Patients requiring these services must undergo a physician screening examination.

Strict federal and state requirements govern the procedure and access to emergency medical care.[5,6,20] An emergency department record on any patient who presents to an emergency department requesting care must be kept for at least five years. In addition, the medical screening examination record must be maintained as long as permanent hospital medical records. We think that hospitals that have followed these prerequisites have a right to refuse further service to patients with nonurgent conditions. A hospital's decision to adopt self-gatekeeping policies will depend on the mission and philosophy of the individual institution, perceived needs and risks, and the perceived effect on community relations. Hospitals may opt to continue their policy of allowing all patients to obtain a physician evaluation and treatment on demand. Emergency physicians have been understandably fearful of the prospect of COBRA liability at the hands of nonphysicians and have been reluctant to share any level of responsibility for the medical screening examination. Given the complexity of busy

emergency departments, however, the patient evaluation is a major enhancement to patient safety and appropriate access. To the extent that this practice is authorized by hospital policy, it should not represent a source of liability for a physician on duty.

Triage Categories

The typical emergency department triage system divides patients into at least three or four tiers, often referred to as emergent, urgent, semiurgent, and nonurgent. Unfortunately, these terms have been misunderstood when used outside of the emergency department context. For example, the term "emergent" is generally used to connote the highest priority and should not imply that patients in an "urgent" category do not require services in the emergency department. This type of semantic confusion has led to arguments between emergency departments and MCOs. To avoid these semantic problems, some emergency departments have chosen numbers or colors to designate triage categories. Common categories include the following:

- *Category I* (obvious emergency): The patient must be examined by a physician as soon as possible. Case examples include cardiac arrest, acute severe chest pain, massive vomiting of blood, sudden loss of consciousness, and major trauma with hypotension.
- *Category II* (strong potential for emergency): The patient will need a full evaluation and treatment by a physician. Case examples include acute dyspnea, acute abdominal pain, acute chest pain, acute confusion, or severe pain.
- *Category III*: The possibility of an occult or pending emergency condition must be considered. The patient must be examined by a physician during the emergency department visit because an emergency cannot be excluded by an initial screening examination.

Most arguments between emergency departments and MCOs occur for patients in category III. Although initially some of these patients may appear to have not-so-serious chief complaints, prospective studies have shown that 25% of these patients have high-risk conditions and many require emergency admission.[29] Identifying this high-risk subset prospectively is difficult. Timely physician care is needed during the patient's visit. Care should be provided in the emergency department; for some conditions, however, care could be provided in an alternative setting such as an adjacent urgent-care area. Case examples for this category include abdominal pain, high fever, acute back pain, serious extremity injuries, and large or high-risk lacerations.

- *Category IV* (nonemergent): There is no reason to think that these patients have an emergency medical condition or are at risk of having one develop. An appointment could be scheduled, or physician care is not required. Disorders are chronic, minor, or self-limiting. Case examples include medication refill, acne, mild adult upper respiratory tract symptoms, mild sore throat, blood pressure check, lumps, and bumps.

Referral to Alternative Care Settings

Most category IV patients need timely access to care after refusal from an emergency department. Despite studies showing the risk versus benefit of referring this category of patients out of an emergency department, the issue continues to be debated by emergency physicians.[22] Two studies allegedly designed to test the safety of referring patients out of an emergency department failed to use a screening examination.[27,28] Detailed arguments for and against the referral of nonemergency patients out of an emergency department can be found elsewhere.[27,30,31] Managed care organization-sponsored alternative care settings for the referral of nonemergency patients need to have facilities and personnel to provide the required service at the same level of skill as would be available in an emergency department.

Intrahospital fast-track clinics provide an alternative to off-site triage for the expeditious treatment of patients with nonemergent conditions. The obvious incentive for referral to a managed care plan's own physician is to save money. In well-integrated prepaid systems, however, where hospital cost shifting is no longer part of the equation, such clinics can provide efficient care and can serve as the predominant point of after-hours access for the episodic needs of otherwise healthy patients.

Summary

Emergency departments serve as America's health care safety net of last resort and will continue to provide federally mandated universal access, despite the powerful influence of managed care in restricting their use. The issue of financial support for this mandate has yet to be resolved. Consumers should understand and assert their rights as patients and plan beneficiaries. Hospitals and their medical and nursing staffs must recognize that they bear the entire responsibility for the provision of emergency care as defined by federal and state law. Managed care organizations and their contracting physicians must accept financial responsibility for the provision of emergency care, and they must educate their enrollees and patients regarding appropriate utilization practices. To the extent that the federal government mandates and contracts for these services, it should monitor quality and facilitate performance by payers as well as providers. On-site triage is an important tool for the organization of emergency department operations. In addition, it can serve as a means for departmental self-gatekeeping and referral to alternative care settings. Hospitals and MCOs must work together to better define emergency conditions, symptoms that are best evaluated in an emergency department, and which patients can be referred directly to MCO primary care physicians.

REFERENCES

1. Goldsmith J: Hospital-physician relationships: A constraint to health reform. Health Aff (Millwood) 1993; 12:160-169

2. Coile RC Jr: Health care 1994 top ten trends for the ERA of health reform. Hosp Strategy Rep 1994; 6:1-7

3. Pogue JF: California physician groups prosper in 'food chain' of managed care. Hosp Strategy Rep 1993; 5:4

4. Derlet RW, Christman C, Ray L, Hamilton B: The impact of managed care organizations on emergency departments (Abstr). Acad Emerg Med 1995; 2:438

5. Medicare Program: Participation in CHAMPUS and CHAMPVA, hospital admissions for veterans, discharge rights notice, and hospital responsibility for emergency care: Interim final rule with comment period. Federal Register 1994; 59:32086-32127

6. Publ L No. 99-272, 42 USC, §1395 dd (1985)

7. 22 California Adm §51056 and Bus Prof Code §2397

8. American College of Emergency Physicians: Definition of an emergency service. Ann Emerg Med 1994; 23:1397

9. Gallagher EJ, Lynn SG: The etiology of medical gridlock: Causes of emergency department overcrowding in New York City. J Emerg Med 1990; 8:785-790

10. Rask KJ, Williams MV, Parker RM, McNagny SE: Obstacles predicting lack of a regular provider and delays in seeking care for patients at an urban public hospital. JAMA 1994; 271:1931-1933

11. Kellermann AL: Nonurgent emergency department visits—Meeting an unmet need (Editorial). JAMA 1994; 271:1953-1954

12. Report on Use of Emergency Rooms by Medicaid Recipients, Office of Evaluation and Inspections publication No. (OEI) 06-90-00180. US Dept of Health and Human Services, Office of Inspector General, March 1992

13. Borzo G: Buying out of the ED—Hospitals, medical staffs paying others to take on-call duty. Am Med News 1992 Oct 12, pp 15-16

14. Lumpe D: Life under managed care. Emerg Med News 1993; 15:14-17

15. Garza MA: 311 summons Louisiana ambulances. J Emerg Med Serv 1994; 19:19-20

16. McCormick B: Surgeons: Managed care traumatic for EDs. Am Med News 1994 Nov 14, pp 5-6

17. Thompson S: The history of HMOs—Have they kept their promise? Calif Physician 1994; 11:62-66

18. Iglehart JK: The American health care system—Medicaid. N Engl J Med 1993; 328:896-900

19. Winesuff J: Medi-Cal managed care: A viable solution? Calif Physician 1994; 11:42-52

20. Cal Health & Safety Code §1317.4, January 1995

21. Medicaid Access Study Group: Access of medicaid recipients to outpatient care. N Engl J Med 1994; 330:1426-1430

22. Derlet RW, Kinser D, Ray L, Hamilton B, McKenzie J: Prospective identification and triage of nonemergency patients out of an emergency department: A five-year study. Ann Emerg Med 1995; 25:215-223

23. McCaig LF: National Hospital Ambulatory Medical Care Survey: 1992 Emergency Department Summary. Vital Health Stat [Advance Data 245] 1994; pp 1-12

24. Buesching DP, Jablonowski A, Vesta E, et al: Inappropriate emergency department visits. Ann Emerg Med 1985; 14:672-676

25. Derlet RW, Nishio D, Cole LM, Silva J Jr: Triage of patients out of the emergency department: Three-year experience. Am J Emerg Med 1992; 10:195-199

26. Mitchell TA: Nonurgent emergency department visits—Whose definition? Ann Emerg Med 1994; 24:961-963

27. Lowe RA, Bindman AB, Ulrich SK, et al: Refusing care to emergency department patients: Evaluation of published triage guidelines. Ann Emerg Med 1994; 23:286-293

28. Birnbaum A, Gallagher EJ, Utkewicz M: Failure to validate a predictive model for refusal of care to emergency-department patients. Acad Emerg Med 1994; 1:213-217

29. Derlet RW, Reynolds J, Kinser D: Initial triage classification does not correlate with retrospective analysis of acuity. Ann Emerg Med 1994; 25:146-147

30. Lowe RA, Bindman AB: The emergency department and triage of nonurgent patients (Letter). Ann Emerg Med 1994; 24:990-991

31. Derlet RW, Kinser D: The emergency department and triage of nonurgent patients (Letter). Ann Emerg Med 1994; 24:991-992

Conferences and Reviews

Biology and Treatment of Adult Acute Lymphoblastic Leukemia

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The molecular analysis of acute lymphoblastic leukemia (ALL) has provided exciting insights into the pathogenesis of this disease. This disease is heterogenous and can be subtyped based on chromosomal, immunophenotypic, and structural criteria. The varying prognostic implications of different ALL subtypes markedly influence the treatment decisions in adults. Many patients with T-cell ALL can be cured with chemotherapy alone. In contrast, patients with early B-lineage ALL with certain chromosomal abnormalities, especially the Philadelphia chromosome, do not have durable responses to chemotherapy and should receive a bone marrow transplantation if an HLA-matched donor is available. Recent reports have shown improved results for adults with B-cell ALL (Burkitt's) after intensive alternating cycles of chemotherapy containing high doses of methotrexate and cyclophosphamide. Future clinical and laboratory investigation should lead to the development of novel and possibly more effective treatments specifically tailored for different subsets of ALL.

(Levitt L, Lin R: Biology and treatment of adult acute lymphoblastic leukemia. West J Med 1996; 164:143-155)

A large amount of information has recently accrued regarding both the biology and the treatment of acute lymphoblastic leukemia (ALL). The molecular analysis of lymphoblasts has provided exciting new information about oncogenesis and the control of cellular proliferation. Intensive regimens of chemotherapy have resulted in cure for a sizable number of patients. New information is available concerning the role of both allogeneic and autologous marrow transplantation in the management of patients with this disease. In this review, we will consider recent advances in the understanding and management of adult ALL.*

Classification

Morphologic Features

Morphologic and immunophenotypic features have traditionally been used to classify patients with ALL. The French-American-British classification recognizes three structural subtypes: L1, L2, and L3.[1] The L1 subtype consists of small uniform lymphoblasts and is found in 25% to 30% of cases of adult ALL. The L2 subtype consists of larger pleomorphic lymphoblasts and is the most common structural subtype found in adults (65% to 70% of cases). The L3 subtype, whose structure resembles that of Burkitt's lymphoma, is usually found in patients with B-cell ALL whose blasts express surface membrane immunoglobulin. The L3 subtype is found infrequently in adults with ALL (2% to 7%).

Immunophenotyping

Monoclonal antibodies and the molecular analysis of surface-receptor gene rearrangements can now be used to more precisely define lineage-specific features of leukemic lymphoblasts.[2,3] Acute lymphoblastic leukemia cells undergo rearrangements of immunoglobulin and T cell-receptor genes and express epitopes of antigen-receptor molecules and differentiation-associated surface glycoproteins in a manner that approximates the events of normal B- and T-lymphocyte development.

B-lineage ALL can be subdivided into at least four subtypes (Table 1). In early pre-B ALL, the lymphoblasts express one or more B lineage-specific surface antigens, but do not have surface or cytoplasmic immunoglobulins. Early pre-B ALL is further divided into two subtypes based on the presence or absence of the common ALL antigen (CD10, or CALLA). The CD10 antigen has recently been identified as a neutral endopeptidase.[4] Early pre-B ALL that is CALLA-positive is the most frequent immunologic subtype in adults with ALL (50% to 60%). Lymphoblasts in this subtype express one or more B lineage-specific antigens (CD19, CD20, and CD22) and usually contain high levels of the enzyme terminal deoxynucleotidyl transferase (TdT).

Early pre-B ALL that is CALLA-negative is found in 10% to 38% of adult patients with ALL.[5-10] In the past,

*See also the editorial by F. R. Appelbaum, MD, "Progress in Adult Acute Lymphoblastic Anemia," on pages 180-181 of this issue.

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ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
BCR = break-point cluster region
CALGB = Cancer and Leukemia Group B [trial]
CALLA = common ALL antigen
CDR-III = complementarity-determining region III
CML = chronic myeloid leukemia
CNS = central nervous system
PCR = polymerase chain reaction
Ph = Philadelphia chromosome
TdT = terminal deoxynucleotidyl transferase

this subtype was labeled null-cell ALL because it expressed neither CD10 nor T lineage-specific surface antigens. With the use of several monoclonal antibodies for early B-lineage surface antigens and molecular analysis for the detection of immunoglobulin gene rearrangements, it is now known that most null-cell blasts are derived from B precursor cells and are a more immature subset than CALLA-positive early pre-B ALL.[11] Early pre-B ALL blasts that are CALLA-negative usually express CD19 and TdT and have rearranged immunoglobulin genes. Immunoglobulin heavy-chain gene rearrangements should not be considered lineage specific because they can be seen in about 15% of patients with T-cell ALL.[12]

Lymphoblasts in the pre-B ALL subtype express B lineage-specific antigens, TdT, and cytoplasmic immunoglobulin heavy chains, but do not express surface immunoglobulin. A specific chromosomal translocation, t(1:19), is found in about a fourth of pre-B cases and is associated with a poor prognosis.[13,14] Little information is available on this immunophenotype in adults with ALL.

B-cell ALL is uncommon in adults (2% to 7%).[5-10] It shares many cytogenetic, immunologic, cytologic, and clinical features with Burkitt's lymphoma.[15] The Burkitt's lymphoblasts often have a distinctive structure characterized by deeply basophilic cytoplasm that contains prominent vacuoles (L3). CD10 may be present on the surface of these cells, although TdT is not usually expressed. Kinetic studies indicate a rapid proliferative potential with in vitro doubling times as short as 26 hours.

About 25% of adults with ALL have T-lineage disease (Table 1).[5-10] T-cell ALL blasts express the prothymocyte antigen CD7 and often additional early or intermediate thymocyte antigens, including CD5, CD2, CD4, and CD8. In 5% to 40% of cases, T-cell ALL blasts express CD10 in combination with other T-cell antigens. T-cell ALL blasts contain TdT and, in most instances, one or more of the T cell-receptor genes are rearranged.[3] Pre–T-cell ALL blasts constitute a more immature T-lineage phenotype and express only surface CD7 and often cytoplasmic CD3 determinants.[10]

Acute mixed-lineage leukemias concurrently express lymphoid as well as myeloid surface antigens. These leukemias are called biphenotypic if they consist of individual blast cells expressing both myeloid (CD13, CD14, or CD33) and lymphoid antigens. Bilineage leukemias consist of two populations of blast cells that express either lymphoid or myeloid antigens.[16] With more detailed immunophenotypic analysis, the incidence of mixed-lineage leukemias appears to be increasing. Overall, myeloid coexpression is found in 10% to 20% of adults with ALL and is seen more often in CALLA-negative early pre-B ALL or pre-T ALL and in patients with unique chromosomal translocations.[17] Recently described assays using monoclonal antibodies to detect the early expression of cytoplasmic proteins such as myeloperoxidase, CD3, CD22, and CD33 may more accurately characterize acute mixed-lineage leukemias.[18] More stringent diagnostic criteria may further enhance the clinical usefulness of this ALL subtype.

Cytogenetic and Molecular Anomalies

Cytogenetic abnormalities are common in patients with ALL and are one of the most important independent prognostic variables for predicting outcome.[19] Recent studies indicate that it may be possible to identify the clonal chromosomal abnormalities in more than 90% of cases of ALL.[20] These chromosomal anomalies may aid in the diagnosis by showing the specific karyotype and often correlate with other clinical features of the disease.

Abnormalities of Cell Ploidy

The distribution of chromosomal ploidy anomalies in

TABLE 1.—*Immunologic Classification of B- and T-Lineage Acute Lymphoblastic Leukemia*

	CD Determinants and Cell Markers					
Classification	*CD19*	*CD10 (CALLA)*	*CD20*	*CytIg*	*SurfIg*	*TdT*
Early pre-B						
CALLA-negative	+	−	−	−	−	+
CALLA-positive	+	+	±	−	−	+
Pre-B cell	+	±	+	+	−	+
B cell	+	±	+	−	+	−
	CD7	*CD5*	*CD2*	*CD1*	*CD4*	*CD8*	*TdT*
Pre-T cell	+	+	±	−	−	−	+
T cell	+	+	+	+	+	+	+

CALLA = common acute lymphoblastic leukemia antigen, CytIg = cytoplasmic immunoglobulin, SurfIg = surface membrane immunoglobulin, TdT = terminal deoxynucleotidyl transferase, + = present, − = absent, ± = may or may not be present

adult ALL is as follows: normal, 15% to 20%; hyperdiploid (>50), 10% to 20%; hyperdiploid (47 to 50), 10%; pseudodiploid (46, abnormal), 30% to 50%; and hypodiploid, 5% to 8%.[21] Patients with hyperdiploid karyotypes appear to have a relatively favorable prognosis, whereas patients with pseudodiploid karyotypes usually have one of several specific chromosomal translocations and have a particularly poor prognosis.[22]

Phenotype-Specific Chromosomal Translocations

The most common chromosomal translocations found in adult patients with ALL include t(9;22)(q34;q11), t(8;14)(q24;q32), t(4;11)(q21;q23), t(1;19)(q23;p13), and translocations with break points near the α-chain locus of the T-cell receptor at 14q11 or near the β-chain locus of the T-cell receptor at 7q35 (Tables 2 and 3).[19,22]

The t(9;22)(q34;q11) translocation, or Philadelphia chromosome (Ph), is found by traditional cytogenetic analysis in about 20% of adults with ALL.[19] Patients with this translocation often fail to achieve remission or have early relapse of their disease. In both chronic myeloid leukemia (CML) and ALL, the c-*abl* gene is translocated from chromosome 9 to chromosome 22.[23] Break points are scattered over more than 175 kilobases (kb) upstream of *abl* exon II. In contrast, breaks on chromosome 22 occur within two limited areas, called the major and minor break-point cluster regions (BCRs).[23] The break points in CML map almost entirely to the major BCR, whereas both the major and minor BCRs appear to be involved in Ph-positive ALL. As a consequence of the translocation, a *BCR-abl* fusion gene is produced that consists of upstream sequences from *BCR* and downstream sequences from *abl*. *BCR-abl* fusion genes with the major BCR break point are transcribed into a chimeric 8.5-kb messenger RNA and produce a p210 *BCR-abl* protein. The *BCR-abl* fusion genes with the minor BCR break point express a chimeric 7.0-kb messenger RNA and a p190 fusion protein. Both fusion proteins exhibit deregulated tyrosine kinase activity.[24,25] Chronic myeloid leukemia has been induced in some transgenic mice expressing p210, and acute leukemia has been seen in some transgenic mice expressing p190.[26,27]

The polymerase chain reaction (PCR) has recently been used to look for *BCR-abl* rearrangements: *BCR-abl* transcripts were found in 43% of adults with ALL, but in only 6% of children with newly diagnosed ALL and 17% of children with relapsed ALL.[28] No rearrangements were found in patients with T-cell disease; 55% of adults with early pre–B-cell ALL were PCR-positive. Two thirds of PCR-positive adults expressed minor BCR break points, and a third expressed BCR break points within the major region. Positivity for PCR correlated with the height of the leukocyte count at presentation and with patient's age.

TABLE 2.—*Characteristic Chromosomal Translocations in Acute Lymphoblastic Leukemia—Translocations Generating Chimeric (Fusion) Proteins*

Translocation	Gene	Phenotype
t(9;22)(q34;q11).....	*BCR-abl*	Early pre-B cell
t(1;19)(q23;p13).....	*E2A-PBX1*	Pre-B cell
t(17;19)(q22;p13).....	*E2A-HLF*	Early pre-B cell
t(4;11)(q21;q23).....	*MLL-AF4*	Early pre-B cell, often with myeloid antigen coexpression
t(11;19)(q23;p13).....	*MLL-ENL*	

TABLE 3.—*Characteristic Chromosomal Translocations in Acute Lymphoblastic Leukemia—Translocations With Rearrangement of an Antigen-Receptor Locus*

Translocation	Gene	Antigen Receptor	Phenotype
t(8;14)(q24;q32).....	c-*myc*	Ig heavy chain	B cell
t(2;8)(p12;q24).....	c-*myc*	Ig κ light chain	B cell
t(8;22)(q24;q11).....	c-*myc*	Ig λ light chain	B cell
t(11;14)(p15;q11).....	*TTG1/RHOM1*	T α/δ locus	T cell
t(1;14)(p32;q11).....	*TAL1/SCL*	T α/δ locus	T cell
t(10;14)(q24;q11).....	*HOX11*	T α/δ locus	T cell
t(7;19)(q35;p13).....	*LYL1*	T β locus	T cell
t(7;9)(q35;q34).....	*TAL2*	T β locus	T cell
t(7;11)(q35;p13).....	*TTG2/RHOM2*	T β locus	T cell

Ig = immunoglobulin

The t(8;14)(q24;q32) translocation is found in patients with B-cell ALL. Variant translocations in B-cell leukemia include t(2;8)(p12;q24) and t(8;22)-(q24;q11).[29] As a consequence of the t(8;14) translocation, the c-*myc* proto-oncogene is transferred from chromosome 8 to the heavy-chain immunoglobulin locus adjacent to the coding sequences for the immunoglobulin constant region. In the variant translocations, c-*myc* remains on chromosome 8, and portions of either the κ (chromosome 2) or λ (chromosome 22) light-chain genes are translocated to regions just downstream of the c-*myc* locus. These translocations appear to disrupt c-*myc* regulation, possibly through repositioning of strong immunoglobulin enhancers adjacent to the c-*myc* locus or in conjunction with c-*myc* mutations that occur coincidentally with the translocation.[30,31] B-cell neoplasms have been induced in transgenic mice that possess c-*myc* driven by an immunoglobulin gene enhancer.[32] Activated c-*myc* is also capable of malignant transformation when it is transfected into human B lymphoblasts infected with the Epstein-Barr virus.[33] It is likely that other genetic anomalies are required for the malignant transformation of B cells in addition to the deregulation of c-*myc* expression.

The t(4;11)(q21;q23) translocation is found in about 5% of adults with ALL.[19,22] Leukemic blasts with this translocation usually have an early pre-B phenotype with rearranged immunoglobulin heavy-chain genes.[34] These cells can be induced to express monocytic features in vitro and can sometimes coexpress myeloid and lymphoid surface antigens in vivo, a characteristic of the mixed-lineage leukemias.[35] The chromosome 11q23 break point, which forms a reciprocal translocation with

chromosome 4 in t(4;11)(q21;q23), is also associated with the t(11;19)(q23;p13) translocation in ALL and is found in almost 10% of cases of acute myelogenous leukemia; the most common translocation seen in acute monocytic leukemia is t(9;11)(p22;q23).[36-38] The 11q23 break point is also seen in ALL patients in whom secondary acute myelogenous leukemia has developed.[39] This region likely contains one or more genes capable of modulating the commitment to lymphoid or myeloid differentiation. Recently, a gene—called *MLL* for mixed-lineage leukemia—was cloned from the 11q23 break point and was found to be a homologue of a *Drosophila trithorax* transcription factor.[40]

The t(1;19)(q23;p13) translocation is found in about 25% of patients with pre–B-cell ALL.[41] This translocation results in a rearrangement of upstream sequences from the *E2A* gene (which codes for a transcriptional regulator protein) on chromosome 19 with downstream sequences from the *PBX1* gene (which codes for a protein with a homeobox DNA-binding domain) on chromosome 1.[13,14] It is possible that the resultant fusion protein could initiate abnormal transcriptional regulation and play a role in leukemogenesis. Recently, the *E2A-PBX1* fusion product has been shown to induce lymphoid proliferation and lymphomas in transgenic mice.[42]

Translocations with break points near the α/δ locus of the T-cell receptor on chromosome 14 (band q11) or the β-chain T cell-receptor locus on chromosome 7 (band q35) have been seen in cases of acute T-cell ALL.[43,44] The t(11;14)(p15;q11) translocation results in a rearrangement of the T-cell receptor α/δ locus with a gene (*TTG1*) on chromosome 11 that codes for a possible DNA-binding zinc-finger transcriptional regulator protein.[45] In an alternative translocation, t(10;14)(q24;q11), the δ locus is rearranged with the *HOX11* proto-oncogene on chromosome 10.[46] The *TAL1* protein is another putative helix-loop-helix transcription factor identified at the translocation break point involving the T cell α/δ-receptor locus—t(1;14)(p32;q11).[47] The *TAL1* rearrangements may be found in as many as 25% of patients with T-cell ALL. The helix-loop-helix transcription factor genes *LYL1* and *TAL2* have been identified at break points involving the 7q35 T-cell β chain-receptor locus—t(7;19)(q35;p13) and t(7;9)(q35;q34), respectively.[44,48] Inversions of the long arm of chromosome 14 involving the α-chain locus at q11 and the immunoglobulin heavy-chain locus at q32 have also been seen in T-cell leukemia.[49]

Clinical Features

A third of adults with ALL present with infections, fever, or both, whereas a third will have hemorrhagic manifestations.[21] Lymphadenopathy and hepatosplenomegaly are seen at presentation in about half of adult patients. Mediastinal masses, sometimes accompanied by pleural effusions, have been reported in 15% of adults with ALL and are most commonly seen in patients with T-cell disease.[21] A few adults (4%) will present with signs or symptoms of central nervous system (CNS) involvement, including headache, vomiting, papilledema, lethargy, nuchal rigidity, or cranial nerve palsies (III, IV, VI, and VII). An additional 3% to 10% of adults will have asymptomatic CNS disease, usually diagnosed by surveillance lumbar puncture and the examination of cytocentrifuged cerebrospinal fluid.

Extramedullary disease in adult patients at other sites at presentation is infrequent. In contrast to children, adults rarely (1% to 2%) have bone or joint pain at diagnosis.[50] Clinical evidence of testicular involvement in adults at presentation is rare (<1%).[21] Isolated testicular relapses to date in adults have proved to be infrequent (1%) and do not warrant surveillance biopsies.[51]

Data on laboratory evaluation at presentation have recently been published following the analysis of two consecutive German multicenter trials involving 938 patients aged 15 to 65 years with ALL.[21] The leukocyte count is elevated ($>10 \times 10^9$ per liter [10,000 per mm^3]) in 59% of adults at presentation. Many adults (27%) will present with leukopenia (leukocyte count $<5 \times 10^9$ per liter [5,000 per mm^3]), and 25% will have an absolute neutrophil count of less than 500×10^6 per liter (500 per mm^3). Hyperleukocytosis (leukocyte count $>100 \times 10^9$ per liter) is found in 16% of adults at diagnosis. Careful examination of the peripheral smear will reveal circulating blasts in 92% of cases. A platelet count below 25×10^9 per liter is found in only 30% of adults at diagnosis, and 80% of adults will have a hemoglobin concentration of less than 120 grams per liter (<12 grams per dl). Recent data indicate that laboratory evidence of a consumptive coagulopathy is seen in 12% of patients before the initiation of chemotherapy and in 78% during remission induction therapy. Serious complications—pulmonary embolus, sagittal sinus thrombosis, hemorrhage—occurred in 34% of these patients.[52] Unusual laboratory manifestations of ALL include eosinophilia, bone marrow necrosis, and cyclic neutropenia.[53-55]

Two ALL immunologic subtypes have clinical features that are rather characteristic. T-cell ALL is frequently associated with high blood leukocyte counts (often more than 100×10^9 per liter), a mediastinal mass, and leptomeningeal leukemia at diagnosis. B-cell ALL is associated with extramedullary sites of disease in the abdomen or head and neck, as well as frequent CNS involvement. The tumor lysis syndrome with hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, disseminated intravascular coagulation, and acute renal failure may accompany the onset of chemotherapy in B-cell ALL.[56]

Prognostic Factors

Data from several recent trials of adult ALL that used different intensive combination chemotherapy regimens have identified similar prognostic factors for remission duration. The most important of these factors appears to be cytogenetic abnormalities, time to achieve complete remission, initial leukocyte count, age, and immunolog-

TABLE 4.—*Adverse Prognostic Features in Acute Lymphoblastic Leukemia*

Indicator	*Unit*
Time to achieve complete remission, wk	>4
Cytogenetic abnormalities	t(9;22), t(4;11)
Leukocyte count, $\times 10^9$/liter (/mm^3)	25-35 (25,000-35,000)
Age, yr	>35
Immunophenotype	Pre-T cell, CALLA-negative early pre-B cell
Mixed lineage	Myeloid antigen coexpression

ic subtype (Table 4).[5,17,19,51,57] In one study, patients at low risk without any of four adverse features—time to remission, >4 weeks; age, >35 years; leukocyte count, >30 $\times 10^9$ per liter; and null-cell immunophenotype—were likely to have a continuous remission rate beyond five years of 62%. Patients with one or more of these adverse features had a predicted five-year relapse-free survival rate of 28%.[51] About 70% of adult ALL patients have one or more of the adverse prognostic factors listed in Table 4. Not all these prognostic factors are necessarily independent of each other. For example, the T-cell immunophenotype portends a good prognosis in adult ALL patients despite the fact that this phenotype is often associated with high leukocyte counts at presentation.

Time to Achieve Complete Remission

The time to achieve complete remission is inversely related to the remission duration. Obtaining complete remission within four or five weeks is associated with a substantially longer remission duration than when additional chemotherapy is required.[51,57] About 75% of adult patients currently achieve a complete remission with intensive chemotherapy; about 10% of these patients require more than four weeks of chemotherapy.

Cytogenetic Abnormalities

An abnormal karyotype (other than hyperdiploidy) is an adverse risk factor independent of other established prognostic factors.[19] The most frequently seen translocations in adult ALL—t(9;22)(q34;q11), t(4;11)(q21;q23)—are associated with a somewhat lower incidence of complete remission and a markedly shorter remission duration.[19,22,28] In a Cancer and Leukemia Group B (CALGB) study, the presence of the *BCR-abl* gene was assessed in adults with ALL using the Southern blot test and pulsed-field gel analysis. Nearly a third (30%) of cases were positive for *BCR-abl*. Although rates of achieving complete remission were similar between *BCR-abl*–positive and –negative groups, there were more early relapses and a shorter remission duration in the *BCR-abl*–positive group.[58] The pronounced disparity in the incidence of the translocation t(9;22)(q34;q11) between children and adults—6% versus 43%, respectively, by PCR analysis—may explain much of the observed difference in survival between these two groups following chemotherapy.[28]

Leukocyte Count

Recent studies indicate that a peripheral leukocyte count at presentation of greater than 25 to 35 $\times 10^9$ per liter is associated with a reduced remission duration in adult patients.[5,8,51] The leukocyte count does not appear to be an independent risk factor and correlates with both age and cytogenetic abnormalities.[28] Clinical leukostasis is rare in patients with ALL, even with leukocyte counts of greater than 100 $\times 10^9$ per liter.

Age

Most studies indicate that increasing age is associated with a shorter remission duration. A recent large study that used intensive combination chemotherapy suggested that being older than 35 was associated with shorter remissions,[51] whereas another large study that used a different protocol of intensive chemotherapy found little difference in relapse rates between patients aged 15 to 25 and those aged 25 to 60; patients older than 60 years had substantially higher relapse rates.[5] In the French Group trial, 58 patients older than 50 were treated with chemotherapy; the three-year disease-free survival rate was 24%.[59] Although many studies do not indicate that age is correlated with rates of achieving remission in adult ALL, contradictory data exist, and when large numbers of patients are included, it appears that there is a continuous decline in complete remission rates with increasing age.[60] In one study, 82% of adults younger than 40 years obtained remission, whereas only 67% of patients 40 to 59 years of age achieved remission, and patients 60 years or older obtained remission only 45% of the time.[61] In a recent series of patients older than 60 with ALL, 22 patients were treated aggressively with curative intent; complete remissions were obtained in only 7 (32%).[62] The higher incidence of karyotypic anomalies and mixed-lineage (biphenotypic) leukemias in older adults may in part explain the worse prognosis in this subgroup of patients with ALL.[28,63]

Immunophenotype

Patients with CALLA-positive early pre–B-cell ALL have traditionally been considered to have the most favorable subtype with regard to remission duration. Recent studies that used intensive chemotherapy, however, suggest that T-cell ALL may now be associated with the most prolonged remission duration.[5,6,9,51,57] In one study, the probability of continuous remission at five years was 59% for adults with T-cell ALL versus 31% for patients with CALLA-positive early pre–B-cell ALL.[57] It is possible that the use of frequent doses of cytarabine with or without cyclophosphamide may in part explain the improved survival of patients with T-cell ALL. T lymphoblasts accumulate high levels of cytarabine triphosphate and exhibit high nucleoside transport activity.[64] Late relapses have been noted as long as five

to six years after achieving complete remission in patients with CALLA-positive ALL, whereas relapses in T-cell ALL usually occur by three years after achieving remission.[57] The CALLA-negative, early pre–B-cell ALL subtype has been associated with a lower five-year relapse-free survival (24%) than either T-cell ALL (55%) or CALLA-positive ALL (34%).[51] Pre–T-cell ALL also appears to show lower responses to treatment than standard T-cell ALL.[10]

Remission rates for adult B-cell ALL (Burkitt's) are only about 40%, and remission durations are often less than 6 to 12 months.[21,65] It is possible that regimens using high doses of cyclophosphamide and methotrexate can increase the likelihood of achieving complete remission and lengthen the duration of remission in adults with B-cell ALL. Recent data indicate that a small number of adults with B-cell ALL treated with frequent cyclic combinations containing such drugs have two- to three-year disease-free survival rates of about 60%.[66-68]

In several studies, adult patients with myeloid antigen expression in early pre–B-cell ALL have a substantially lower likelihood of achieving complete remission (29% to 50%) than those patients whose blasts do not coexpress myeloid antigens (71% to 83%).[17,63,69,70] A CALGB cooperative trial prospectively studied 76 adults with ALL and identified myeloid-lymphoid antigen coexpression in 33% of cases. No differences in response or survival were seen between myeloid-positive and -negative patients expressing T-cell antigens. Among patients expressing B-cell antigens, however, myeloid-positive patients had fewer complete remissions and shorter survival.[63] Three subsequent single-institution studies comprising 40 to 62 patients also indicate that myeloid coexpression is associated with a poorer complete remission rate and a shorter remission duration.[69-71] Not all studies have found a prognostic importance for myeloid antigen coexpression, however, and this subject remains controversial.[72]

Detection of Minimal Residual Disease

Traditional morphologic methods of detecting minimal residual leukemia have not been sufficiently sensitive to detect leukemic cells constituting less than 2% to 5% of bone marrow mononuclear cells. Immunophenotyping, DNA flow cytometry, cytogenetics, and leukemic colony assays have also shown limited sensitivity and specificity for detecting minimal residual leukemia.[73] A number of alternative methods have recently been used in efforts to detect very small numbers of residual leukemic cells in the marrow of ALL patients during clinical remission.

Immunoglobulin or T cell-receptor gene rearrangement analysis has permitted the detection of 1 leukemic cell in as few as 500 normal mononuclear nucleated cells in the bone marrow of patients with ALL.[74] The use of the PCR to amplify leukemia-specific chromosomal translocations has increased the sensitivity for detecting minimal residual disease by three to four orders of magnitude.[73] The high incidence of the *BCR-abl* rearrangement using PCR analysis in adults with ALL may, for example, prove useful for the assessment of residual disease in many patients with early pre–B-cell ALL. The PCR has recently been used to assess *BCR-abl* minimal residual disease following marrow transplantation in patients with Ph-positive ALL. The detection of the *BCR-abl* transcripts by PCR preceded clinical relapse by three to nine weeks in eight patients; seven other patients have remained in remission with no evidence of minimal residual disease by PCR.[75] These results differ from those in patients with CML, in whom persistent *BCR-abl* transcripts are not always a sign of clinical relapse.[76] Many leukemia-specific chromosomal translocations have yet to be molecularly characterized, thus limiting the routine application of this method.

An alternative, albeit technically demanding, approach uses the clonal expansion of unique DNA sequences (the hypervariable complementarity-determining region III [CDR-III] of the immunoglobulin heavy chain) in B cell-lineage lymphoblasts.[77] Rearrangements of these sequences can be used as markers of the leukemic clone. In this method, PCR is used to amplify unique CDR-III sequences in leukemic blasts using primers that are homologous to consensus sequences in regions that flank the rearranged segment in the heavy-chain locus. The leukemia-specific CDR-III–amplified segments are then sequenced and used to generate diagnostic oligonucleotide probes.[77] This method, which is potentially applicable to most instances of B-lineage ALL, can detect 1 leukemic cell in a population of 100,000 normal cells. CDR-III–based PCR amplification has been used to assess minimal residual disease in a group of 181 patients with ALL.[78] The detection of disease by this clone-specific technique appeared to correlate with clinical outcome, and the extent of residual disease was related to the probability of relapse. Analogous clone-specific probes have also been generated for PCR in cases of T-cell ALL.[79] The main limitations of these techniques include the need to generate sequence-specific probes and the possibility that target gene rearrangements may be unstable during clonal evolution. It is likely that the adequacy and duration of ALL treatment, however, will in the future be determined in part by careful and sensitive assessments of minimal residual disease.

Treatment

Chemotherapy

Induction. The remission rate achieved in adults with the use of vincristine and prednisone alone is only 40% to 60%, and the use of this regimen has been associated with short remission durations despite the use of varied consolidation and maintenance regimens.[80] In a retrospective study from the Netherlands, administering vincristine and prednisone alone resulted in a complete remission rate of 46%, whereas the use of vincristine and prednisone plus daunorubicin achieved a complete remission rate of 68%.[81] A prospective, randomized

study by CALGB showed a complete remission rate of 47% (25/52) in adults given induction therapy with vincristine, prednisone, and asparaginase, whereas a regimen that used the same three medications plus daunorubicin resulted in a complete remission rate of 83% (38/46).[82] Remission rates of at least 70% to 80% have been achieved in most recent series of adult ALL using vincristine, prednisone, and an anthracycline with or without asparaginase.[21]

The use of high-dose cytarabine in combination with an induction regimen of vincristine, prednisone, and doxorubicin in de novo ALL does not result in a complete remission rate superior to that achieved with conventional treatment.[83] Similarly, administering either high-dose cytarabine alone or an anthracycline plus standard-dose cytarabine does not appear to result in better overall survival rates than conventional induction regimens in de novo ALL.[83-85] Such an approach may prove beneficial, however, in subsets of high-risk patients with ALL.

B-cell ALL does not respond well to conventional ALL induction regimens.[65] A different induction regimen using alternating cycles of high-dose cyclophosphamide, methotrexate, and cytarabine is recommended for patients with this subtype of ALL.[66-68]

Central nervous system therapy. Leukemic involvement of the CNS is present at diagnosis in about 10% of adults with ALL.[6,7,9] Risk factors for CNS disease include T-cell disease, Burkitt's leukemia, and an elevated leukocyte count (>50 × 10^9 per liter).[86] The treatment of documented CNS disease usually consists of the intrathecal administration of methotrexate in combination with cranial irradiation.[87] Some investigators recommend placing an Ommaya reservoir to administer chemotherapy intraventricularly, although no studies have provided definitive support for this approach.[88] With adequate treatment, the presence of CNS leukemia at diagnosis does not appear to adversely influence relapse-free survival rates in adult patients with ALL.[51,57]

The incidence of CNS leukemic relapse at one year was 21% in a series of adults with ALL who received intensive chemotherapy without CNS prophylaxis.[86] In a randomized trial of cranial irradiation plus intrathecal methotrexate, the incidence of CNS relapse was reduced from 32% to 11% and the predicted two-year CNS relapse rate from 42% to 19%.[89] No difference was found between the two groups in hematologic remission duration or survival, however. The standard approach to CNS prophylaxis is to use intrathecal methotrexate plus cranial irradiation.[87] Alternative approaches—such as high systemic doses of cytarabine or methotrexate—do not appear to be superior to the combined use of intrathecal methotrexate plus cranial irradiation and may be associated with enhanced neurotoxicity, particularly in older patients.[81,90] Minimal neuropsychological toxicity has been reported in adults following CNS prophylaxis with intrathecal methotrexate plus cranial irradiation.[91] It seems reasonable to administer CNS prophylaxis to adults after achieving a complete remission, with the understanding that its role remains to be precisely defined and that the full effects of CNS prophylaxis may not be apparent in adults with ALL until its use is assessed in the context of more effective systemic therapy.

Continuation (postremission) chemotherapy. Consolidation or intensification chemotherapy refers to early treatment after obtaining remission with combinations of drugs of comparable intensity to induction chemotherapy, usually given in repeated courses over several months. Maintenance therapy refers to lower-dose treatment, usually given continuously for several years. Two small randomized studies support the use of consolidation or intensification therapy in adults with ALL. A French study randomly assigned 61 patients in remission to receive or not receive intensification therapy with doxorubicin, cytarabine, and asparaginase, administered monthly for three cycles. Disease-free survival at three years favored those patients receiving intensification, 38% versus 0%.[92] A European Organization for the Treatment of Cancer (EORTC) study randomly assigned 65 ALL patients in remission to receive either four months of intensive consolidation or one month of less intensive treatment: the median duration of complete remission favored those patients receiving the more intensive consolidation regimen, 45 versus 24 months.[93] A recent randomized CALGB study, however, failed to demonstrate benefit for two daunorubicin-plus-cytarabine consolidation cycles compared with the use of mercaptopurine plus methotrexate only.[94]

A number of uncontrolled studies using intensive consolidation regimens support the use of aggressive postremission chemotherapy in adults with ALL. The Memorial Sloan-Kettering Cancer Center (New York, NY; protocols L2 through L17M) has reported complete remission in 82% of 199 adults (median age, 25) and a disease-free survival rate at ten years of 38%.[6] A German multicenter study of 368 patients (median age, 25) achieved a remission rate of 74% and a ten-year disease-free survival rate of 35%.[95] A Stanford–University of California, San Francisco–City of Hope (Duarte, California) study of 109 adults (median age, 25) reported an 88% remission rate and a disease-free survival rate at five years of 42%.[57] Comparable results have been obtained in a number of other large trials in adults with ALL using a variety of consolidation programs.[10,59,96] High-dose cytarabine or methotrexate has been used in recent postinduction regimens; although these regimens may result in improved outcomes for certain high-risk subsets of adults, the results need to be confirmed in larger groups of patients.[95]

The treatment of patients with Ph-positive ALL remains a difficult problem. With intensified induction regimens, complete remission rates of 70% can be obtained in these patients.[58] The three-year disease-free survival rate in one study, however, was 8% for *BCR-abl*–positive patients compared with 59% for *BCR-abl*–negative patients.[95] High-dose cytarabine in consolidation may prove beneficial.[95] A small number of patients has been successfully maintained with interferon alfa.[97]

After the completion of consolidation therapy, most patients receive standard continuation chemotherapy with relatively low doses of oral methotrexate and mercaptopurine until two to three years after obtaining complete remission. Although considerable evidence supports the use of maintenance chemotherapy in children, the efficacy of this approach in adults is not as clear.[98] It is likely that most adults with standard early pre–B-cell or T-cell ALL benefit from some form of maintenance therapy; conversely, maintenance does not seem to play an important role in the current management of patients with Burkitt's B-cell ALL or Ph-positive ALL.

Relapsed and resistant leukemia. Second remissions can be achieved in about 50% of adults who relapse, either with the same drugs that were used to induce the initial remission or with alternative combinations of chemotherapy.[99] Second remissions are more commonly obtained in adults who relapse after the completion of maintenance chemotherapy than in those who relapse while still receiving chemotherapy.

A number of alternative chemotherapeutic regimens have been studied in resistant ALL, that is, in patients who fail to achieve remission with standard induction chemotherapy. Moderate to high doses of methotrexate—given incrementally from a starting dose of 200 mg per m^2 to as much as 6 grams followed by rescue with leucovorin calcium (folinic acid)—with or without asparaginase have been reported to achieve response rates of 33% to 75% in patients with resistant ALL.[100,101] Adults tolerate this regimen poorly and experience considerable gastrointestinal and hematologic toxic reactions, especially with the asparaginase combination. Administering amsacrine plus high-dose cytarabine has been reported to achieve a complete remission in 27 of 36 (75%) adults with relapsed ALL and in 2 of 4 adults with resistant leukemia.[102] A regimen of mitoxantrone plus high-dose cytarabine produced a complete remission rate of 38% (13/34) in adults with refractory ALL.[103] The use of a combination of prednisone, intermediate-dose cytarabine, mitoxantrone, and etoposide (PAME) has been shown to achieve a complete remission in 30 of 43 (70%) adult patients with relapsed or resistant ALL.[104] The prognosis of relapsed or refractory ALL is grim, however, with the median remission duration after salvage treatment of less than six months and a three-year disease-free survival rate of less than 5% to 10%.[21]

Long-term sequelae of treatment. Long-term sequelae of multiagent chemotherapy in adults with ALL have recently been assessed now that prolonged survival following therapy has become a reality for many patients. Intensive chemotherapy results in transient azoospermia in almost all men; spermatogenesis appears to recover in most patients, however, after the completion of consolidation therapy.[105] Male endocrine gonadal function does not appear to be impaired after the administration of intensive combination chemotherapy for ALL. In female patients with ALL, neither reproductive nor gonadal endocrine functions appear to be impaired following chemotherapy.[105] As in children, an increased incidence of acute myelogenous leukemia associated with chromosomal translocations involving 11q23 has been reported in adults who received prolonged exposure to epipodophyllotoxins for the treatment of ALL.[106] Avascular necrosis of bone has also been reported in adults with ALL, which may be related to the administration of combination chemotherapy regimens that include high doses of corticosteroids.[107]

Bone Marrow Transplantation

Allogeneic marrow transplantation. Allogeneic marrow transplantation, usually performed with marrow donated from an HLA-identical sibling, is an effective strategy in the treatment of adults with ALL.[108] Because of higher-dose intensity of the preparative regimen and the probable antileukemic effect mediated by the graft-versus-leukemia phenomenon, ALL patients treated with allogeneic transplantation generally have lower rates of relapse than comparable groups of patients receiving intensive combination chemotherapy.[109] Allogeneic transplantation, however, is associated with considerable morbidity and mortality as a consequence of immunosuppression, graft-versus-host disease, opportunistic infections, and toxicity from the preparative regimens.[110] Patients older than 60 years are generally not considered candidates for allogeneic transplantation. Given the small family sizes in North America, only about 30% of otherwise eligible patients in the United States have HLA-compatible sibling donors.[111]

Transplantations for advanced ALL in relapse result in a 10% to 20% long-term disease-free survival.[108] These results are superior to those for chemotherapy, but clearly the procedure benefits only a small number of patients. The disease-free survival rate for patients with ALL in second remission at three to five years following allogeneic transplantation is 32% to 52% (average, 36%); this outcome is also clearly superior to that achieved with chemotherapy, which has a disease-free survival rate at three years of only about 5% to 10%.[108,112-115] Although no randomized prospective trials have directly compared the two strategies in adults with ALL, it is likely that patients younger than 60 in second remission with a suitable donor will benefit from allogeneic transplantation, regardless of the duration of their first remission.

The treatment strategy for adults with ALL in first remission is more controversial. Data from the International Bone Marrow Transplant Registry, the European Bone Marrow Transplantation Group, and a number of additional transplantation centers indicate a 43% to 71% (average, 50%) disease-free survival rate two or more years following allogeneic marrow transplantation for adults in first complete remission.[59,108,114,116-119] Many of these patients have had one or more high-risk features, including a leukocyte count of greater than 25×10^9 per liter, older than 30 years, chromosomal translocations, or a requirement for prolonged therapy to achieve remission.

In a high-risk subgroup, patients with Ph-positive ALL, allogeneic marrow transplantation for a patient in first complete remission appears superior to administering chemotherapy alone, which has a disease-free survival rate of less than 10%. In one study, the disease-free survival rate at two years was 38% when 33 patients had transplantation during their first complete remission, 41% when transplantation was done during relapse, and 25% in refractory patients.[120]

A retrospective comparison of chemotherapy recipients and recipients of HLA-identical sibling allogeneic transplants for ALL in first remission was performed by the International Bone Marrow Transplant Registry.[109] Chemotherapy recipients were treated in 44 German hospitals according to an intensive regimen previously reported.[51] After statistical adjustments for differences in prognostic variables and time to treatment, survival was similar in the two cohorts: the five-year disease-free survival rate was 38% with chemotherapy and 44% after transplantation. Although these results were not statistically significant, patients receiving transplants had an unusually high transplantation-related mortality of 39%. Factors predicting relapse appeared to be similar for both groups of patients. No specific prognostic subgroup had an improved survival with one treatment compared with the other. In a prospective study of postremission therapy in 436 adult ALL patients achieving first remission, allogeneic transplantation resulted in a three-year disease-free survival rate of 43%.[59] This result was not significantly different from that achieved for 95 patients who received an autologous transplant (39% disease-free survival) or 96 patients who received chemotherapy (32% disease-free survival). More large prospective trials will be required to resolve the issue of optimal therapy for varying subsets of adults with ALL in first remission. Allogeneic marrow transplantation may also be useful in some ALL patients who never achieve remission even with intensive chemotherapy. In a series of 38 such patients, the disease-free survival rate at three years was 23% (37% in patients younger than 30).[121]

Transplants from HLA-identical sibling donors are available in only a few patients with ALL. Matched-unrelated donor transplantation has been done in ALL patients at various stages of disease.[122] These transplants are associated with increased morbidity and mortality from graft-versus-host disease. Currently, the role of matched-unrelated donor transplantation in the treatment of ALL remains undefined.

Autologous marrow transplantation. Autologous marrow can be harvested from ALL patients during remission, then reinfused following preparative treatment with high-dose chemotherapy with or without irradiation. Although this procedure avoids the risks of graft-versus-host disease and the need for prolonged immunosuppression, autologous transplants are associated with much higher relapse rates compared with allogeneic transplants. This is probably due to contamination of transplanted marrow with residual leukemic cells and a lack of a graft-versus-leukemia effect from an allogeneic graft.

The harvested marrow is often treated before cryopreservation in an attempt to purge the specimen of residual leukemic cells. A number of methods have been used to purge ALL remission bone marrow, including administering monoclonal antibodies directed against B-cell or T-cell differentiation antigens, mafosfamide, etoposide, and perfosfamide (4-hydroperoxycyclophosphamide).[123-126] It is not clear which if any of these procedures is effective in eradicating minimal residual leukemia.

Adults who have received an autologous transplant in second remission have disease-free survival rates ranging from 15% to 29% (average, 23%) at three years.[112,125,127-129] These results are superior to those achieved with chemotherapy alone. Again, no randomized trials have been done that directly compare these two strategies. Many patients salvaged in first relapse are not candidates for an autologous transplantation due to age, poor performance status, or organ dysfunction. Selection bias makes it difficult to directly compare autologous transplantation results with historical controls treated with chemotherapy. Nonetheless, given the poor long-term prognosis of adults who receive chemotherapy after a first relapse, it is reasonable to consider patients in their second complete remission without an HLA-matched donor as candidates for an autologous transplant. Autologous transplantations ideally should be performed as soon as possible after achieving a second remission.

In early studies, disease-free survival in adults in first remission following autologous transplantation appeared promising, with rates of 32% to 65% (average, 41%).[119,123,124,127,128] Prospective trials to date, however, demonstrate no advantage of consolidation treatment with an autologous transplant over chemotherapy. In the French Group trial, patients without an allogeneic donor were randomly assigned to receive autologous transplantation or intensification with chemotherapy. The disease-free survival rate based on intention-to-treat analysis for 95 patients receiving an autologous transplant was 39%, and that for 96 patients receiving chemotherapy was 32%; this difference was not significant.[59] For the 63 patients who actually received an autologous transplant in their first remission, the three-year disease-free survival rate was 51%. It appears premature at this time to recommend autologous marrow transplantation for adults with ALL in first complete remission. It is likely that improved conditioning regimens, more effective methods for eradicating marrow residual disease ex vivo, and immunomodulation after transplantation will make autologous transplantation a more promising procedure for high-risk adults with ALL in first remission. The treatment results for adults with ALL following either chemotherapy or allogeneic or autologous transplantation are summarized in Table 5.* Recommendations for managing adults with ALL in first remission are given in Table 6.[130,131]

*References 5, 9, 57-59, 65-67, 95, 96, 112-119, 123-125, and 127-129.

TABLE 5.—*Treatment of Adult Acute Lymphoblastic Leukemia (ALL) With Chemotherapy and Allogeneic or Autologous Bone Marrow Transplantation*

Treatment	Probability of Disease-Free Survival at 3-5 Yr, %	
	1st Complete Remission	2nd Complete Remission
Chemotherapy		
T cell	45-60*	5-10
CALLA-positive, early pre-B cell	30-35*	5-10
CALLA-negative, early pre-B cell	20-25*	5-10
B cell	10-60†	5-10
Ph-positive ALL	<10‡	5-10
Allogeneic transplant	50§ (43-71)‖	36§ (32-52)¶
Autologous transplant	41§ (32-65)#	23§ (15-29)**

CALLA = common ALL antigen, Ph = Philadelphia chromosome

*From Gaynor et al,[5] Hussein et al,[9] Linker et al,[57] and Kantarjian et al.[96]

†From Gill et al,[65] Fenaux et al,[66] and Pees et al.[67]

‡From Linker et al,[57] Westbrook et al,[58] and Hoelzer.[95]

§Weighted average = Σ disease-free survival × No. of patients in the study ÷ total No. of patients.

‖From Fière et al,[59] Gratwohl et al,[114] Vernant et al,[116] Chao et al,[117] Mrsic et al,[118] and Blaise et al.[119] N = 514.

¶From Arcese et al,[112] Weyman et al,[113] Gratwohl et al,[114] and Blume et al.[115] N = 467.

#From Fière et al,[59] Blaise et al,[119] Simonsson et al,[123] Gilmore et al,[124] Gorin et al,[127] and Rizzoli et al.[128] N = 435.

**From Arcese et al,[112] Soiffer et al,[125] Gorin et al,[127] Rizzoli et al,[128] and Doney et al.[129] N = 185.

Peripheral blood stem-cell transplantation. Peripheral blood stem cells can be harvested from patients in remission using leukapheresis after stimulating with cytotoxic chemotherapy and recombinant growth factors. Studies have shown that the number of hematopoietic progenitors harvested with this method can exceed those obtained with a bone marrow harvest.[132] These "mobilized" stem cells are then used to reconstitute the marrow in patients treated with marrow ablative chemotherapy.[133] Recent data suggest that preferential harvesting of *BCR-abl*–negative peripheral stem cells may be possible during early recovery from chemotherapy-induced hypoplasia in chronic myeloid leukemia.[134] This technology may possibly be used as a "purging" technique in the treatment of patients with Ph- positive ALL and other subtypes of ALL with identifiable cytogenetic or molecular markers.[135]

Conclusions

The immunophenotypic and molecular characterization of lymphoblasts in ALL has provided important insights into the nature of leukemogenesis. Advances in the understanding of the disease have resulted in improved methods of diagnosis, more accurate prognostic criteria, and more sensitive means for detecting minimal residual disease. Intensive combination chemotherapy and bone marrow transplantation now offer the possibility of cure for a substantial number of adults. Future investigation will need to more precisely define the indications for chemotherapy versus allogeneic, autologous, or peripheral stem-cell transplantation in the treatment of ALL. Specific treatment regimens will need to be more clearly and individually defined for different disease subsets. It is probable that further characterization of the disordered gene regulation found in ALL lymphoblasts will lead to an improved understanding of the disease's pathogenesis. Furthermore, a better understanding of the genetic basis of ALL may allow the implementation of novel therapies targeted at the underlying molecular or biochemical abnormalities found within the lymphoblast.

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukaemias—French-American-British (FAB) co-operative group. Br J Haematol 1976; 33:451-458

2. Foa R, Migone N, Saitta M, et al: Different stages of B cell differentiation in non-T acute lymphoblastic leukemia. J Clin Invest 1984; 74:1756-1763

3. Waldmann TA: The arrangement of immunoglobulin and T cell receptor genes in human lymphoproliferative disorders. Adv Immunol 1987; 40:247-321 (350 ref)

4. Jongeneel CV, Quackenbush EJ, Ronco P, Verroust P, Carrel S, Letarte M: Common acute lymphoblastic leukemia antigen expressed on leukemia and melanoma cell lines has neutral endopeptidase activity. J Clin Invest 1989; 83:713-717

5. Gaynor J, Chapman D, Little C, et al: A cause-specific hazard rate analysis of prognostic factors among 199 adults with acute lymphoblastic leukemia: The Memorial Hospital experience since 1969. J Clin Oncol 1988; 6:1014-1030 [erratum published in J Clin Oncol 1988; 6:1522]

6. Radford JE Jr, Burns CP, Jones MP, et al: Adult acute lymphoblastic leukemia: Results of the Iowa HOP-L protocol. J Clin Oncol 1989; 7:58-66

7. Linker CA, Levitt LJ, O'Donnell M, et al: Improved results of treatment of adult acute lymphoblastic leukemia. Blood 1987; 69:1242-1248

8. Gingrich RD, Burns CP, Armitage JO, et al: Long-term relapse-free survival in adult acute lymphoblastic leukemia. Cancer Treat Rep 1985; 69:153-160

TABLE 6.—*Adults With Acute Lymphoblastic Leukemia (ALL) in First Complete Remission—Recommendations for Treatment*

ALL Subtype	Recommendations
T cell	Aggressive postremission chemotherapy; no allogeneic transplant unless relapse. For patients without HLA-matched sibling donors, consider cryopreserving remission marrow or peripheral blood progenitor cells to use in case of relapse
B cell	Chemotherapy using high doses of cyclophosphamide and methotrexate in combination with an anthracycline, cytarabine, and teniposide; no allogeneic transplantation unless relapse. For patients without HLA-matched sibling donors, consider cryopreserving remission marrow or peripheral blood progenitor cells for use in case of relapse
Early pre-B cell	Allogeneic transplantation in first CR for patients who have chromosomal translocations—other than t(8;14)(q24;q32)—or who require more than 4-5 wk to enter CR. Aggressive postremission chemotherapy for rest of patients and allogeneic transplantation if relapse occurs and HLA-matched sibling donor available. Consider cryopreserving first remission marrow or peripheral blood progenitor cells if no allogeneic donor available
Ph-positive	Allogeneic transplantation in first CR; if no allogeneic donor available, consider high-dose cytarabine for consolidation followed by interferon alfa; or entry into phase I-II trials (for example, therapy targeting the fusion gene product by engineered ribozymes or antisense oligomeres)*

CR = complete remission, HLA = human leukocyte antigen, Ph = Philadelphia chromosome

*From Shore et al[130] and Skórski et al.[131]

9. Hussein KK, Dahlberg S, Head D, et al: Treatment of acute lymphoblastic leukemia in adults with intensive induction, consolidation, and maintenance chemotherapy. Blood 1989; 73:57-63

10. Thiel E, Kranz BR, Raghavachar A, et al: Prethymic phenotype and genotype of pre-T (CD7+/ER−)-cell leukemia and its clinical significance within adult acute lymphoblastic leukemia. Blood 1989; 73:1247-1258

11. First MIC Cooperative Study Group: Morphologic, immunologic, and cytogenetic (MIC) working classification of acute lymphoblastic leukemias—Report of the workshop held in Leuven, Belgium, April 22-23, 1985. Cancer Genet Cytogenet 1986; 23:189-197

12. Kitchingman GR, Rovigatti U, Mauer AM, Melvin S, Murphy SB, Stass S: Rearrangement of immunoglobulin heavy chain genes in T cell acute lymphoblastic leukemia. Blood 1985; 65:725-729

13. Nourse J, Mellentin JD, Galili N, et al: Chromosomal translocation t(1;19) results in synthesis of a homeobox fusion mRNA that codes for a potential chimeric transcription factor. Cell 1990; 60:535-545

14. Kamps MP, Murre C, Sun XH, Baltimore D: A new homeobox gene contributes the DNA binding domain of the t(1;19) translocation protein in pre-B ALL. Cell 1990; 60:547-555

15. Bouffet E, Frappaz D, Pinkerton R, Favrot M, Philip T: Burkitt's lymphoma: A model for clinical oncology. Eur J Cancer 1991; 27:504-509

16. Gale RP, Ben Bassat I: Hybrid acute leukaemia. Br J Haematol 1987; 65:261-264

17. Drexler HG, Thiel E, Ludwig WD: Review of the incidence and clinical relevance of myeloid antigen-positive acute lymphoblastic leukemia. Leukemia 1991; 5:637-645

18. Vaickus L, Ball ED, Foon KA: Immune markers in hematologic malignancies. Crit Rev Oncol Hematol 1991; 11:267-297

19. Bloomfield CD, Secker-Walker LM, Goldman AI, et al: Six-year follow-up of the clinical significance of karyotype in acute lymphoblastic leukemia. Cancer Genet Cytogenet 1989; 40:171-185

20. Williams DL, Raimondi S, Rivera G, George S, Berard CW, Murphy SB: Presence of clonal chromosome abnormalities in virtually all cases of acute lymphoblastic leukemia (Letter). N Engl J Med 1985; 313:640-641

21. Hoelzer D: Acute lymphoblastic leukemia in adults, *In* Hoffman R, Benz E, Shattil S, Furie B, Cohen H (Eds): Hematology: Basic Principles and Practice. New York, NY, Churchill Livingstone, 1991, pp 793-804

22. Hagemeijer A, van der Plas DC: Clinical relevance of cytogenetics in acute leukemia. Hamatol Bluttransfus 1990; 33:23-30

23. Kurzrock R, Gutterman JU, Talpaz M: The molecular genetics of Philadelphia chromosome-positive leukemias. N Engl J Med 1988; 319:990-998

24. Konopka JB, Watanabe SM, Witte ON: An alteration of the human c-*abl* protein in K562 leukemia cells unmasks associated tyrosine kinase activity. Cell 1984; 37:1035-1042

25. Kurzrock R, Shtalrid M, Romero P, et al: A novel c-*abl* protein product in Philadelphia-positive acute lymphoblastic leukaemia. Nature 1987; 325: 631-635

26. Daley GQ, Van Etten RA, Baltimore D: Induction of chronic myelogenous leukemia in mice by the P210 *bcr/abl* gene of the Philadelphia chromosome. Science 1990; 247:824-830

27. Heisterkamp N, Jenster G, ten Hoeve J, Zovich D, Pattengale PK, Groffen J: Acute leukaemia in *bcr/abl* transgenic mice. Nature 1990; 344: 251-253

28. Maurer J, Janssen JW, Thiel E, et al: Detection of chimeric BCR-ABL genes in acute lymphoblastic leukaemia by the polymerase chain reaction. Lancet 1991; 337:1055-1058

29. Klein G: Specific chromosomal translocations and the genesis of B-cell–derived tumors in mice and men. Cell 1983; 32:311-315

30. Taub R, Kelly K, Battey J, et al: A novel alteration in the structure of an activated c-*myc* gene in a variant t(2;8) Burkitt lymphoma. Cell 1984; 37: 511-520

31. Adams JM, Gerondakis S, Webb E, Corcoran LM, Cory S: Cellular *myc* oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. Proc Natl Acad Sci USA 1983; 80:1982-1986

32. Adams JM, Harris AW, Pinkert CA, et al: The c-*myc* oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. Nature 1985; 318:533-538

33. Lombardi L, Newcomb EW, Dalla-Favera R: Pathogenesis of Burkitt lymphoma: Expression of an activated c-*myc* oncogene causes the tumorigenic conversion of EBV-infected human B lymphoblasts. Cell 1987; 49:161-170

34. Mirro J, Kitchingman G, Williams D, et al: Clinical and laboratory characteristics of acute leukemia with the 4;11 translocation. Blood 1986; 67: 689-697

35. Stong RC, Korsmeyer SJ, Parkin JL, Arthur DC, Kersey JH: Human acute leukemia cell line with the t(4;11) chromosomal rearrangement exhibits B lineage and monocytic characteristics. Blood 1985; 65:21-31

36. Huret JL, Brizard A, Slater R, et al: Cytogenetic heterogeneity in t(11;19) acute leukemia: Clinical, hematological and cytogenetic analyses of 48 patients—Updated published cases and 16 new observations. Leukemia 1993; 7:152-160

37. Diaz MO, Le Beau MM, Pitha P, Rowley JD: Interferon and c-*ets*-1 genes in the translocation (9;11)(p22;q23) in human acute monocytic leukemia. Science 1986; 231:265-267

38. Abe R, Sandberg AA: Significance of abnormalities involving chromosomal segment 11q22-25 in acute leukemia. Cancer Genet Cytogenet 1984; 13:121-127

39. Pui CH, Behm FG, Raimondi SC, et al: Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Engl J Med 1989; 321:136-142

40. Thirman MJ, Gill HJ, Burnett RC, et al: Rearrangement of the *MLL* gene in acute lymphoblastic and acute myeloid leukemias with 11q23 chromosomal translocations. N Engl J Med 1993; 329:909-914

41. Carroll AJ, Crist WM, Parmley RT, Roper M, Cooper MD, Finley WH: Pre-B cell leukemia associated with chromosome translocation 1;19. Blood 1984; 63:721-724

42. Dedera D, Waller E, LeBrun DP, et al: Chimeric homeobox gene *E2A-PBX1* induces proliferation, apoptosis, and malignant lymphomas in transgenic mice. Cell 1993; 74:833-843

43. Croce CM, Isobe M, Palumbo A, et al: Gene for α-chain of human T-cell receptor: Location on chromosome 14 region involved in T-cell neoplasms. Science 1985; 227:1044-1047

44. Mellentin JD, Smith SD, Cleary ML: *lyl-1*, a novel gene altered by chromosomal translocation in T cell leukemia, codes for a protein with a helix-loop-helix DNA binding motif. Cell 1989; 58:77-83

45. McGuire EA, Hockett RD, Pollock KM, Bartholdi MF, O'Brien SJ, Korsmeyer SJ: The t(11;14)(p15;q11) in a T-cell acute lymphoblastic leukemia cell line activates multiple transcripts, including *Ttg-1*, a gene encoding a potential zinc finger protein. Mol Cell Biol 1989; 9:2124-2132

46. Kagan J, Finger LR, Letofsky J, Finan J, Nowell PC, Croce CM: Clustering of breakpoints on chromosome 10 in acute T-cell leukemias with the t(10;14) chromosome translocation. Proc Natl Acad Sci USA 1989; 86: 4161-4165

47. Chen Q, Cheng JT, Tasi LH, et al: The *tal* gene undergoes chromosome translocation in T cell leukemia and potentially encodes a helix-loop-helix protein. EMBO J 1990; 9:415-424

48. Reynolds TC, Smith SD, Sklar J: Analysis of DNA surrounding the breakpoints of chromosomal translocations involving the β T cell receptor gene in human lymphoblastic neoplasms. Cell 1987; 50:107-117

49. Denny CT, Yoshikai Y, Mak TW, Smith SD, Hollis GF, Kirsch IR: A chromosome 14 inversion in a T-cell lymphoma is caused by site-specific recombination between immunoglobulin and T-cell receptor loci. Nature 1986; 320:549-551

50. Rossi JF, Bataille R, Chappard D, Alexandre C, Janbon C: B cell malignancies presenting with unusual bone involvement and mimicking multiple myeloma—Study of nine cases. Am J Med 1987; 83:10-16

51. Hoelzer D, Thiel E, Löffler H, et al: Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 1988; 71:123-131

52. Sarris AH, Kempin S, Berman E, et al: High incidence of disseminated intravascular coagulation during remission induction of adult patients with acute lymphoblastic leukemia. Blood 1992; 79:1305-1310

53. Bachhuber R, Fitchen JH, Harty-Golder B: Rash and eosinophilia in a 23-year-old man—Oregon Health Sciences University (Clinicopathologic Conference). West J Med 1982; 137:221-227

54. Niebrugge DJ, Benjamin DR: Bone marrow necrosis preceding acute lymphoblastic leukemia in childhood. Cancer 1983; 52:2162-2164

55. Lensink DB, Barton A, Appelbaum FR, Hammond WP 4th: Cyclic neutropenia as a premalignant manifestation of acute lymphoblastic leukemia. Am J Hematol 1986; 22:9-16

56. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL: Acute tumor lysis syndrome—A review of 37 patients with Burkitt's lymphoma. Am J Med 1980; 68:486-491

57. Linker CA, Levitt LJ, O'Donnell M, Forman SJ, Ries CA: Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: A follow-up report. Blood 1991; 78:2814-2822

58. Westbrook CA, Hooberman AL, Spino C, et al: Clinical significance of the *BCR-ABL* fusion gene in adult acute lymphoblastic leukemia: A Cancer and Leukemia Group B Study (8762). Blood 1992; 80:2983-2990

59. Fière D, Lepage E, Sebban C, et al: Adult acute lymphoblastic leukemia: A multicentric randomized trial testing bone marrow transplantation as post-remission therapy—The French Group on Therapy for Adult Acute Lymphoblastic Leukemia. J Clin Oncol 1993; 11:1990-2001

60. Barnett MJ, Greaves MF, Amess JA, et al: Treatment of acute lymphoblastic leukaemia in adults. Br J Haematol 1986; 64:455-468

61. Henderson ES, Scharlau C, Cooper MR, et al: Combination chemotherapy and radiotherapy for acute lymphocytic leukemia in adults: Results of CALGB protocol 7113. Leuk Res 1979; 3:395-407

62. Taylor PR, Reid MM, Bown N, Hamilton PJ, Proctor SJ: Acute lymphoblastic leukemia in patients aged 60 years and over: A population-based study of incidence and outcome. Blood 1992; 80:1813-1817

63. Sobol RE, Mick R, Royston I, et al: Clinical importance of myeloid antigen expression in adult acute lymphoblastic leukemia. N Engl J Med 1987; 316:1111-1117

64. Plunkett W, Liliemark JO, Estey E, Keating MJ: Saturation of ara-CTP accumulation during high-dose ara-C therapy: Pharmacologic rationale for intermediate-dose ara-C. Semin Oncol 1987; 14(suppl 1):159-166

65. Gill PS, Meyer PR, Pavlova Z, Levine AM: B cell acute lymphocytic leukemia in adults—Clinical, morphologic, and immunologic findings. J Clin Oncol 1986; 4:737-743

66. Fenaux P, Lai JL, Miaux O, Zandecki M, Jouet JP, Bauters F: Burkitt cell acute leukaemia (L3 ALL) in adults: A report of 18 cases. Br J Haematol 1989; 71:371-376

67. Pees HW, Radtke H, Schwamborn J, Graf N: The BFM-protocol for HIV-negative Burkitt's lymphomas and L3 ALL in adult patients: A high chance for cure. Ann Hematol 1992; 65:201-205

68. McMaster ML, Greer JP, Greco FA, Johnson DH, Wolff SN, Hainsworth JD: Effective treatment of small-noncleaved-cell lymphoma with high-intensity, brief-duration chemotherapy. J Clin Oncol 1991; 9:941-946

69. Urbano-Ispizua A, Matutes E, Villamor N, et al: Clinical significance of the presence of myeloid associated antigens in acute lymphoblastic leukaemia. Br J Haematol 1990; 75:202-207

70. Guyotat D, Campos L, Shi ZH, et al: Myeloid surface antigen expression in adult acute lymphoblastic leukemia. Leukemia 1990; 4:664-666

71. Childs CC, Hirsch-Ginsberg C, Walters RS, et al: Myeloid surface antigen-positive acute lymphoblastic leukemia (My+ ALL): Immunophenotypic, ultrastructural, cytogenetic, and molecular characteristics. Leukemia 1989; 3:777-783

72. Preti A, Huh Y, O'Brien S, et al: Prognostic significance of positive myeloid markers in adult ALL (Abstr). Blood 1993; 82:57a

73. Hirsch-Ginsberg C, Huh YO, Kagan J, Liang JC, Stass SA: Advances in the diagnosis of acute leukemia. Hematol Oncol Clin North Am 1993; 7:1-46

74. Zehnbauer BA, Pardoll DM, Burke PJ, Graham ML, Vogelstein B: Immunoglobulin gene rearrangements in remission bone marrow specimens from patients with acute lymphoblastic leukemia. Blood 1986; 67:835-838

75. Miyamura K, Tanimoto M, Morishima Y, et al: Detection of Philadelphia chromosome-positive acute lymphoblastic leukemia by polymerase chain reaction: Possible eradication of minimal residual disease by marrow transplantation. Blood 1992; 79:1366-1370

76. Hughes TP, Morgan GJ, Martiat P, Goldman JM: Detection of residual leukemia after bone marrow transplant for chronic myeloid leukemia: Role of polymerase chain reaction in predicting relapse. Blood 1991; 77:874-878

77. Yamada M, Hudson S, Tournay O, et al: Detection of minimal disease in hematopoietic malignancies of the B-cell lineage by using third-complementarity-determining region (CDR-III)-specific probes. Proc Natl Acad Sci USA 1989; 86:5123-5127

78. Brisco MJ, Condon J, Hughes E, et al: Outcome prediction in childhood acute lymphoblastic leukaemia by molecular quantification of residual disease at the end of induction. Lancet 1994; 343:196-200

79. Kneba M, Bolz I, Linke B, Bertram J, Rothaupt D, Hiddemann W: Characterization of clone-specific rearranged T-cell receptor γ-chain genes in lymphomas and leukemias by the polymerase chain reaction and DNA sequencing. Blood 1994; 84:574-581

80. Hess CE, Zirkle JW: Results of induction therapy with vincristine and prednisone alone in adult acute lymphoblastic leukemia: Report of 43 patients and review of the literature. Am J Hematol 1982; 13:63-71

81. Willemze R, Hillen H, Hartgrink-Groeneveld CA, Haanen C: Treatment of acute lymphohlastic leukemia in adolescents and adults: A retrospective study of 41 patients (1970-1973). Blood 1975; 46:823-834

82. Gottlieb AJ, Weinberg V, Ellison RR, et al: Efficacy of daunorubicin in the therapy of adult acute lymphocytic leukemia: A prospective randomized trial by cancer and leukemia group B. Blood 1984; 64:267-274

83. Rohatiner AZ, Bassan R, Battista R, et al: Intensive chemotherapy for acute lymphoblastic leukaemia in adults. Hamatol Bluttransfus 1990; 33: 413-418

84. Arlin Z, Feldman E, Ahmed T, et al: After 25 years with vincristine/prednisone, have we found a better induction therapy for ALL? (Abstr) Blood 1991; 78:447a

85. Kasparu H, Sreter L, Holowiecki J, et al: Intensified induction therapy for ALL in adults: A multicenter trial. Onkologie 1991; 14(suppl 1):80

86. Kantarjian HM, Walters RS, Smith TL, et al: Identification of risk groups for development of central nervous system leukemia in adults with acute lymphocytic leukemia. Blood 1988; 72:1784-1789

87. Bleyer WA, Poplack DG: Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin Oncol 1985; 12:131-148

88. Bleyer WA, Poplack DG: Intraventricular versus intralumbar methotrexate for central-nervous-system leukemia: Prolonged remission with the Ommaya reservoir. Med Pediatr Oncol 1979; 6:207-213

89. Omura GA, Moffitt S, Vogler WR, Salter MM: Combination chemotherapy of adult acute lymphoblastic leukemia with randomized central nervous system prophylaxis. Blood 1980; 55:199-204

90. Bleyer WA: CNS Leukemia, *In* Henderson ES, Lister TA (Eds): Leukemia, 5th edition. Philadelphia, Pa, WB Saunders, 1990, pp 733-768

91. Tucker J, Prior PF, Green CR, et al: Minimal neuropsychological sequelae following prophylactic treatment of the central nervous system in adult leukaemia and lymphoma. Br J Cancer 1989; 60:775-780

92. Fière D, Extra JM, David B, et al: Treatment of 218 adult acute lymphoblastic leukemias. Semin Oncol 1987; 14(suppl 1):64-66

93. Stryckmans P, De Witte T, Bitar N, et al: Cytosine arabinoside for induction, salvage, and consolidation therapy of adult acute lymphohlastic leukemia. Semin Oncol 1987; 14(suppl 1):67-72

94. Ellison RR, Mick R, Cuttner J, et al: The effects of postinduction intensification treatment with cytarahine and daunorubicin in adult acute lymphocytic leukemia: A prospective randomized clinical trial by Cancer and Leukemia Group B. J Clin Oncol 1991; 9:2002-2015

95. Hoelzer D: Treatment of acute lymphohlastic leukemia. Semin Hematol 1994; 31:1-15

96. Kantarjian HM, Walters RS, Keating MJ, et al: Results of the vincristine, doxorubicin, and dexamethasone regimen in adults with standard- and high-risk acute lymphocytic leukemia. J Clin Oncol 1990; 8:994-1004

97. Ohyashiki K, Ohyashiki JH, Tauchi T, et al: Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia: A pilot study which raises important questions. Leukemia 1991; 5:611-614

98. Miller DR: Acute lymphoblastic leukemia. Pediatr Clin North Am 1980; 27:269-291

99. Freund M, De Bohen M, Diedrich H, et al: Treatment of relapsed acute lymphocytic leukemia in adults. Hamatol Bluttransfus 1990; 33:432-436

100. Yap BS, McCredie KB, Keating MJ, Bodey GP, Freireich EJ: Asparaginase and methotrexate combination chemotherapy in relapsed acute lymphoblastic leukemia in adults. Cancer Treat Rep 1981; 65(suppl 1):83-87

101. Peterson BA, Bloomfield CD: High-dose methotrexate for the remission induction of refractory adult acute lymphocytic leukemia. Med Pediatr Oncol 1978; 5:79-84

102. Arlin ZA, Feldman E, Kempin S, et al: Amsacrine with high-dose cytarabine is highly effective therapy for refractory and relapsed acute lymphoblastic leukemia in adults. Blood 1988; 72:433-435

103. Kantarjian HM, Estey EH, O'Brien S, et al: Intensive chemotherapy with mitoxantrone and high-dose cytosine arabinoside followed by granulocyte-macrophage colony-stimulating factor in the treatment of patients with acute lymphocytic leukemia. Blood 1992; 79:876-881

104. Milpied N, Gisselbrecht C, Harousseau JL, et al: Successful treatment of adult acute lymphohlastic leukemia after relapse with prednisone, intermediate-dose cytarabine, mitoxantrone, and etoposide (PAME) chemotherapy. Cancer 1990; 66:627-631

105. Kreuser ED, Hetzel WD, Heit W, et al: Reproductive and endocrine gonadal functions in adults following multidrug chemotherapy for acute lymphoblastic or undifferentiated leukemia. J Clin Oncol 1988; 6:588-595

106. Rugo HS, Ries CA, Levitt LJ, O'Donnell M, Foreman S, Linker C: Risk of myeloid relapse from intensive cyclical chemotherapy containing teniposide for adult ALL (Abstr). Proc Am Soc Clin Oncol 1994; 13:307

107. Chan-Lam D, Prentice A, Copplestone J: Avascular necrosis of bone following intensified steroid therapy for ALL and high-grade lymphoma. Br J Haematol 1994; 86:227-230

108. Bortin MM, Horowitz MM, Rowlings PA, et al: 1993 progress report from the International Bone Marrow Transplant Registry—Advisory Committee of the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1993; 12:97-104

109. Horowitz MM, Messerer D, Hoelzer D, et al: Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. Ann Intern Med 1991; 115:13-18

110. Sutton L, Kuentz M, Cordonnier C, et al: Allogeneic bone marrow transplantation for adult acute lymphoblastic leukemia in first complete remission: Factors predictive of transplant-related mortality and influence of total body irradiation modalities. Bone Marrow Transplant 1993; 12:583-589

111. Beatty PG, Hansen JA, Longton GM, et al: Marrow transplantation from HLA-matched unrelated donors for treatment of hematologic malignancies. Transplantation 1991; 51:443-447

112. Arcese W, Amadori S, Meloni G, et al: Allogeneic or Autologous Bone Marrow Transplantation for Intensification of Salvage Therapy in Patients with High-Risk Advanced Acute Lymphoblastic Leukemia. Semin Hematol 1991; 28:116-121

113. Weyman C, Graham-Pole J, Emerson S, et al: Use of cytosine arahinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphoblastic leukemia: A multicenter survey. Bone Marrow Transplant 1993; 11:43-50

114. Gratwohl A, Hermans J, Zwaan F: BMT for ALL in Europe, *In* Gale R, Hoelzer D (Eds): Acute Lymphoblastic Leukemia. New York, NY, Wiley-Liss, 1990, pp 271-278

115. Blume KG, Schmidt GM, Chao NJ, Forman SJ: Bone marrow transplantation from histocompatible sibling donors for patients with acute lymphoblastic leukemia. Hamatol Bluttransfus 1990; 33:636-637

116. Vernant JP, Marit G, Maraninchi D, et al: Allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia in first complete remission. J Clin Oncol 1988; 6:227-231

117. Chao NJ, Forman SJ, Schmidt GM, et al: Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia during first complete remission. Blood 1991; 78:1923-1927

118. Mrsic M, Nemet D, Labar B, et al: Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia. Transplant Proc 1993; 25:1268-1270

119. Blaise D, Gaspard MH, Stoppa AM, et al: Allogeneic or autologous bone marrow transplantation for acute lymphoblastic leukemia in first complete remission. Bone Marrow Transplant 1990; 5:7-12

120. Barrett AJ, Horowitz MM, Ash RC, et al: Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 1992; 79:3067-3070

121. Biggs JC, Horowitz MM, Gale RP, et al: Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. Blood 1992; 80:1090-1093

122. Busca A, Anasetti C, Anderson G, et al: Unrelated donor or autologous marrow transplantation for treatment of acute leukemia. Blood 1994; 83: 3077-3084

123. Simonsson B, Burnett AK, Prentice HG, et al: Autologous bone marrow transplantation with monoclonal antibody purged marrow for high risk acute lymphoblastic leukemia. Leukemia 1989; 3:631-636

124. Gilmore MJ, Hamon MD, Prentice HG, et al: Failure of purged autologous bone marrow transplantation in high risk acute lymphoblastic leukaemia in first complete remission. Bone Marrow Transplant 1991; 8:19-26

125. Soiffer RJ, Roy DC, Gonin R, et al: Monoclonal antibody-purged autologous bone marrow transplantation in adults with acute lymphoblastic leukemia at high risk of relapse. Bone Marrow Transplant 1993; 12:243-251

126. Auber ML, Horwitz LJ, Blaauw A, et al: Evaluation of drugs for elimination of leukemic cells from the bone marrow of patients with acute leukemia. Blood 1988; 71:166-172

127. Gorin NC, Aegerter P, Auvert B: Autologous bone marrow transplantation for acute leukemia in remission: An analysis of 1322 cases. Hamatol Bluttransfus 1990; 33:660-666

128. Rizzoli U, Mangoni L, Carella AM, et al: Drug-mediated marrow purging: Mafosfamide in adult acute leukemia in remission—The experience of the Italian study group. Bone Marrow Transplant 1989; 4(suppl 1):190-194

129. Doney K, Buckner CD, Fisher L, et al: Autologous bone marrow transplantation for acute lymphoblastic leukemia. Bone Marrow Transplant 1993; 12:315-321

130. Shore SK, Nabissa PM, Reddy EP: Rihozyme-mediated cleavage of the BCR-ABL oncogene transcript: In vitro cleavage of RNA and in vivo loss of P210 protein-kinase activity. Oncogene 1993; 8:3183-3188

131. Skórski T, Nieborowska-Skórska M, Barletta C, et al: Highly efficient elimination of Philadelphia leukemic cells by exposure to *bcr/abl* antisense oligodeoxynucleotides combined with mafosfamide. J Clin Invest 1993; 92: 194-202

132. Siena S, Bregni M, Brando B, Ravagnani F, Bonadonna G, Gianni AM: Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: Enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. Blood 1989; 74:1905-1914

133. Chao NJ, Schriber JR, Grimes K, et al: Granulocyte colony-stimulating factor 'mobilized' peripheral blood progenitor cells accelerate granulocyte and platelet recovery after high-dose chemotherapy. Blood 1993; 81:2031-2035

134. Carella AM, Podesta M, Frassoni F, et al: Selective overshoot of Ph-negative blood hemopoietic cells after intensive idarubicin-containing regimen and their repopulating capacity after reinfusion. Stem Cells 1993; 3:67-72

135. Carella AM, Pollicardo N, Pungolino E, et al: Mobilization of cytogenetically 'normal' blood progenitors cells by intensive conventional chemotherapy for chronic myeloid and acute lymphoblastic leukemia. Leuk Lymphoma 1993; 9:477-483

Conferences and Reviews

Malignant Melanoma and Pregnancy
Ten Questions

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Eight patient case vignettes are presented to illustrate the possible relationship between melanoma and pregnancy. We pose 10 questions regarding the risk and prognosis and answer them based on information in the medical literature. Key conclusions are that there is no evidence that the risk for melanoma is influenced by pregnancy; there is no evidence that abortion in pregnant women diagnosed with melanoma is therapeutic for the mother or necessary to prevent melanoma in the fetus; although as a group, pregnant women diagnosed with melanoma may have a somewhat worse prognosis compared with nonpregnant controls, this difference disappears when patients are matched for factors including age, location and depth of primary, or stage of disease; and there is still a concern that pregnant women may present with more invasive or advanced disease due to hormonal or growth factor effects or delays in diagnosis because changes are attributed to pregnancy.

(Dillman RO, VanderMolen LA, Barth NM, Bransford KJ: Malignant melanoma and pregnancy—Ten questions. West J Med 1996; 164:156-161)

During the past 20 years, the incidence of malignant melanoma has steadily increased to the extent that several authors have referred to a "melanoma epidemic."[1,2] In 1994 it was estimated that melanoma would account for 3% of all invasive cancers (32,000 cases), 2% of all cancer deaths in men (4,300 cases), and 1% of all cancer deaths in women (2,600 cases).[3] Although these numbers are relatively low compared with those of tobacco-related cancers, it is noteworthy that between 1973 and 1989, melanoma was second only to female lung cancer in the greatest percentage increase in both cancer incidence (80.6%) and cancer deaths (32.1%) in the United States.[4] Sun exposure and hereditary factors appear to play an important role in the increased risk of melanoma, but other environmental and biologic factors may be important as well.[5] Early diagnosis is probably the most important factor related to the improved survival rates noted over the past 40 years.[5,6]

For many years, there has been concern over the relationship of melanoma to pregnancy, including the documentation of numerous cases of melanoma appearing or progressing during pregnancy.[7-13] The incidence of melanoma during pregnancy has been estimated at 2.8 to 5 per 100,000 pregnancies.[14,15] In 1970 it was suggested that melanoma accounted for 8% of all cases of cancer seen in pregnancy.[16] This is not surprising because about a third of all American women are in the childbearing age range of 15 to 45, and melanoma is not infrequent in this age group. For many years, the concern has been that the hormonal and immunologic changes that take place in pregnancy may be important in the evolution or progression of melanoma.[17] Some aspects of pregnancy are associated with varying degrees of immunosuppression, which may be important for avoiding rejection of the embryo. Donegan has noted that "normal pregnancy and cancer are the only two biologic conditions in which antigenic tissue is tolerated by a seemingly intact immune system."[18(p194)] In addition, the relationship between adrenocorticothyrotropic hormone and melanocyte-stimulating hormone in melanoma, as well as other evidence of melanocyte stimulation, has heightened concern for a possible causal relationship between pregnancy and melanoma. In this article, we briefly describe several recent cases of melanoma that appeared or progressed during pregnancy, and we review the literature that establishes the current concepts regarding the prognosis of patients with melanoma in pregnancy and the risk of pregnancy in women who have had melanoma.

Report of Cases

The following patients were previously diagnosed with melanoma while nulligravida and then were found to have metastatic disease during or shortly after their first pregnancy.

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Patient 1

The patient, a 29-year-old woman, had a family history of melanoma. At age 27 she had a pigmented lesion excised from her right lower leg. Although the lesion was initially interpreted as having only moderate atypical melanocytic hyperplasia, a second opinion described "severe atypia," and a wide excision was done. In April 1991, she was found to be pregnant and had a therapeutic abortion in May. At that time, right inguinal lymphadenopathy was discovered that progressed over the next several months. Iliac adenopathy and a left supraclavicular lymph node also developed. Biopsies confirmed the presence of metastatic melanoma. She then had a complete response to a regimen of carmustine, cisplatin, dacarbazine, and tamoxifen citrate and is currently maintained in complete remission with interferon alfa, tamoxifen, and cimetidine.

Patient 2

The patient, a 30-year-old woman, at age 25 had a melanoma of unknown depth, Clark's level II, removed from the sole of her left foot. She had never been pregnant. In 1989 and 1990, she underwent abortions. In 1991 she took progestational agents for several months. In August 1992, she delivered a full-term infant. In December 1992, she was found to have widely metastatic melanoma involving the liver, spine, abdomen, and lungs. She had no response to dacarbazine chemotherapy and died in February 1993.

Patient 3

The patient, a 30-year-old woman, gravida 1, para 1, at age 20 had a mole removed from her left upper back in 1982. A diagnosis of melanoma was made. In February 1992, she delivered a normal infant, but she had noted a progressive cough for several months. This persisted and led to a chest roentgenogram that disclosed parenchymal masses. On biopsy, the masses were found to be melanoma. She subsequently received interleukin-2 only, then interleukin-2 and tumor-infiltrating lymphocytes, then a regimen of carmustine, cisplatin, dacarbazine, and tamoxifen. She responded to none of these therapies and died in January 1993, five months after diagnosis.

The following previously pregnant women had melanoma appear during a subsequent pregnancy.

Patient 4

A 40-year-old woman who had previously had an abortion was found to have a pigmented lesion on her back in 1990 during her second pregnancy. This pigmented lesion was noted to enlarge and bleed, but regressed postpartum. Two years later, in 1992, she presented with multiple lymph node metastases in the supraclavicular, axillary, and mediastinal regions. Biopsies revealed metastatic melanoma. The original, presumed primary, lesion was noted to be flattened, with vitiligo surrounding it. She had an excellent response to a regimen of carmustine, cisplatin, dacarbazine, and tamoxifen. This was followed by interferon alfa maintenance therapy. She subsequently progressed but failed to respond to the administration of interleukin-2, interleukin-2 plus interferon gamma, or to carmustine and carboplatin. She died 14 months after the original diagnosis.

Patient 5

This 35-year-old woman, gravida 6, para 5, noted bleeding from a mole on her right posterior thigh during her first trimester in December 1986. She alleged that she had brought the bleeding to the attention of two different physicians in that month and the following month and was reassured that this was caused by swelling related to her pregnancy. In June 1987, she had a normal delivery but was noted to have a melanoma of the upper posterior thigh. A 14 × 7 mm lesion was resected that was 5 mm deep, Clark's level IV. She underwent a wider excision and did well until September 1989, when she presented with a 4-cm right groin mass. A right radical inguinal lymph node dissection was done, with a finding of 2 of 13 lymph nodes positive for cancer. No treatment was given, and in March 1990, she was found to have a metastatic lesion on the lip and lung metastases. She was then treated with interferon alfa, then dacarbazine and cisplatin, but the disease progressed. Bone metastases developed, and she died in January 1991.

Patient 6

The patient, a 34-year-old woman, noticed a mole on her upper outer arm that grew during her fourth pregnancy. She miscarried, and the lesion regressed. In 1991, two months into another pregnancy, she again became aware of the mole but was allegedly reassured that it need not be excised. At the time of delivery, however, her obstetrician recommended that the lesion be removed. Two months later, October 1991, this was resected and found to be a melanoma of unknown depth. She did well until a year later, when she noted some dizziness, leading to magnetic resonance imaging and a neurosurgical procedure, with the finding of metastatic melanoma. Additional staging revealed multiple bone metastases. She was treated with carmustine, cisplatin, dacarbazine, interferon alfa, and tamoxifen, after completing a course of cranial irradiation. She died of progressive disease in November 1993.

The following parous woman was diagnosed during pregnancy with metastatic melanoma of an unknown primary.

Patient 7

The patient, a 30-year-old woman, gravida 2, para 1, had no previous history of melanoma. At 34 weeks of gestation, she presented with brain metastases. She had a viable infant who was delivered by cesarean section. The placenta showed invasion with melanoma, but the baby was uninvolved. No primary melanoma lesion was found. Additional staging revealed liver and lung metastases. She had a good partial response to a regimen of carmustine, cisplatin, dacarbazine, and tamoxifen chemohormonal therapy, but leptomeningeal disease developed, and the patient died within five months of diagnosis.

The following patient had melanoma previously diagnosed during pregnancy, and metastatic disease developed during a subsequent pregnancy.

Patient 8

This patient had term pregnancies at ages 19 and 22. During the second pregnancy, she had a pigmented lesion removed from the left leg that was initially interpreted as atypical melanocytic hyperplasia and then as melanoma in situ. A wider excision was done. At age 24, four months into a third pregnancy, she was found to have left inguinal lymphadenopathy; a biopsy was done, and histologic examination showed melanoma. She elected to terminate the pregnancy and underwent inguinal lymphadenectomy. She also enrolled in a trial of placebo versus allogeneic vaccine. The patient was still without evident disease 15 months later.

Discussion

Ten Questions

1. Does pregnancy increase the risk of subsequently having melanoma?

Six case-controlled studies have evaluated the influence of previous pregnancy on the subsequent risk of melanoma.[19-24] None of these studies suggested an increased risk, and two actually suggested that women with three or more children had a lower melanoma risk than nulliparous women.

2. Is there an increased risk of melanoma developing during pregnancy?

There is no convincing evidence that there is an increased risk of melanoma developing during pregnancy. In 1951 the suggestion was made that "some benign nevi are incited to undergo malignant degeneration during pregnancy."[25(p334)] Melanoma is occasionally diagnosed during pregnancy, and some have speculated that the hormonal and immunosuppressive effects of pregnancy may induce malignant transformation.[26,27] No population studies have shown that the risk of melanoma is higher in women during pregnancy, although melanoma may be more likely to be diagnosed during pregnancy because of closer medical observation. A cross-analysis of Connecticut Tumor Registry and live-birth records revealed that the percentage of pregnant women with melanoma was the same as that of nonpregnant women with melanoma.[28] The reported association of apparent transformation of a known nevus into melanoma appears to be about the same for pregnant women, 62% to 68% of melanomas,[7,29] as for men and women in the general population, 65% of melanomas.[7,30] Because of hormonal effects, it has been suggested that preexisting nevi may grow and become more noticeable during pregnancy, but malignant change during pregnancy is thought to be no greater than that for the general population.[31] In conclusion, there is no evidence to support the idea that pregnancy increases the risk of a primary melanoma lesion developing. The standard of care, however, is that any suspicious change in a pigmented cutaneous lesion during pregnancy still warrants doing a biopsy.[18]

3. Is a previous pregnancy associated with a more favorable outcome for women subsequently diagnosed with melanoma?

Efforts to address this question have resulted in conflicting data. In one study, 330 parous women with melanoma were compared with 113 nulliparous women with melanoma.[32] The previously pregnant women had a superior five-year survival rate, 77% versus 68%. The survival advantage was even greater for the subset of women older than 50 (73% versus 53%) and was most impressive overall in those with stage I disease (84% versus 53%). Another study suggested improved survival for women younger than 50 who had been pregnant at least five times; this difference was not explained by other variables such as the Breslow or Clark's level of disease.[33] In contrast, two other trials found no difference for nulliparous versus parous women in five-year survival rates (63% versus 61%) who had melanoma,[34] nor in five- or nine-year survival rates for patients with stage I melanoma (87% versus 83%).[35] Another retrospective study also found no difference in survival between nulliparous and parous women with stage I disease in whom there was no history of disseminated melanoma activation during a previous pregnancy.[36] Although this may be a provocative question, it may be irrelevant from a health care standpoint. It is unlikely that anyone is going to suggest that women have or not have pregnancies because of a possible change in outcome for a future melanoma that may never occur.

4. Do women who are diagnosed with localized melanoma during pregnancy have a worse prognosis?

It was suggested more than 40 years ago that women diagnosed with localized melanoma during pregnancy may have a worse prognosis than nonpregnant women with localized disease.[25] It was claimed that melanomas that developed during pregnancy

> grow with unusual rapidity and metastasize widely. Women diagnosed with localized melanoma during pregnancy may have a worse prognosis than nonpregnant women with localized disease. The prognosis of pregnant women with melanoma is bad and few cures are obtained.[25(p334)]

Other investigators came to the same conclusion in a small retrospective study of 18 women diagnosed with melanoma during pregnancy compared with 12 women who earlier had been diagnosed with melanoma and later became pregnant,[37] although this is obviously not a comparable control group. Numerous recent studies have failed to demonstrate any worse prognosis for pregnant patients with melanoma when patients are adequately matched for age, primary site, and stage of disease, especially by depth of the primary melanoma.[7,22,36,38,39] There is a tendency in many of these studies for pregnant patients with melanoma to have more advanced disease as a group than controls, however, necessitating adjustment for stage and even depth of disease.

In contrast, a retrospective analysis at Duke University School of Medicine (Durham, North Carolina) found a

shorter relapse-free interval for 58 women diagnosed with melanoma during pregnancy than in 855 nonpregnant control patients with melanoma.[40] A series of analyses of a prospective study at the same university of 100 women aged 18 to 40 diagnosed with melanoma during pregnancy have continued to show that these women have a higher risk of metastases developing by ten years (48% versus 26%, $P = .01$) than do women who were not pregnant when the diagnosis was made.[9,41] These differences persisted even after controlling for tumor site, Breslow level, and Clark's level. So far, there has been no difference in overall survival in this group of patients, perhaps because the most dramatic differences noted have been in the frequency of regional lymph node metastases, and some of the women may have been rescued by surgical treatment. In fact, long-term survival for these patients approaches that of the normal population. Based on these results, the Duke group has suggested that elective prophylactic or diagnostic lymph node dissection be carried out in pregnant women diagnosed with melanoma. The issue of whether pregnant women with newly diagnosed localized melanoma are at higher risk for subsequent manifestation of metastatic disease could be clarified by carefully designed, prospective, controlled trials, with control groups for several variables.

Some recent retrospective analyses have shed light on this issue. In a study of 92 patients diagnosed with melanoma during pregnancy, their outcome was compared with that of 85 women who had been diagnosed with melanoma before their first pregnancy, 143 who had melanoma diagnosed after completing all pregnancies, and 68 women in whom melanoma developed between pregnancies.[39] The women who were diagnosed during pregnancy had a significantly worse overall survival ($P < .017$, log rank) and disease-free survival, but the mean tumor thickness in the group was 2.38 mm compared with 1.49 mm for those diagnosed before pregnancy, 1.96 mm for those diagnosed after ceasing childbearing, and 1.48 mm for those who were diagnosed with melanoma between pregnancies ($P = .002$, Pearson's χ^2 test). When a log rank adjustment was made for this difference in depth, the survival differences disappeared. At five years, it appears that survival is worse for those diagnosed with melanoma while pregnant and for those diagnosed after completing all pregnancies, which represents an older age group. In terms of disease-free survival, those who were pregnant had a worse outcome.

In another recent large, retrospective study, 66 patients who were diagnosed with melanoma while pregnant were compared with 619 matched female melanoma patients, including 66 nonpregnant women matched by age, primary site, stage, and histopathologic variables.[42] The five-year survival rates were 86% to 92% for all three groups, and there was no significant difference between any of the groups.

In summary, as a group, women diagnosed with melanoma may have a worse outcome compared with nonpregnant women, but if so, the difference is related to a more invasive stage of disease at the time of diagnosis.

5. Do women with regional or metastatic melanoma diagnosed during pregnancy have a worse prognosis?

Metastatic melanoma is associated with a poor prognosis, with patients who have regional lymph node disease having a five-year survival rate of only about 30% and those with distant metastatic disease having a five-year survival rate of 15%.[43] No studies suggest that outcome is worse for pregnant patients with advanced melanoma once they are matched with controls for the extent of disease.[28,38] Although such patients are fortunately rare, several investigators have suggested that pregnant patients are more likely to develop or already have regional lymph node metastases at the time of diagnosis than are nonpregnant controls.[9,23,41,44] Also, as noted earlier, there seems to be a tendency for pregnant patients with melanoma to have somewhat more deeply invasive primary disease as a group at the time of diagnosis than do control patients. Whether this is due to the natural history of melanoma in a pregnant patient, however, or whether it may be due to delays in diagnosis because of the tendency to attribute earlier signs of melanoma to the effects of pregnancy is unclear. No one has examined risk variables and done a multivariate analysis to determine whether pregnancy itself is a risk factor for more advanced disease.

6. Is there a risk of transplacental metastases to the fetus?

There definitely is a risk of transplacental transmission of melanoma from mother to fetus, but fortunately this risk is low.[45,46] Placental involvement itself is indicative of widespread hematogenous dissemination in the mother, but placental involvement does not necessarily mean that the newborn baby will have melanoma. Of 35 cases of placental or fetal involvement with cancer following pregnancy, one study found that 11 were due to melanoma, the most common cancer associated with this phenomenon, followed by leukemia or lymphoma.[47] Of the 11 melanoma patients, the placenta was involved in 7 and the fetus in 6. Two of the infants with melanoma underwent spontaneous regression of disease after delivery. It has been suggested that only 25% of infants with placental metastatic melanoma will actually die of metastatic melanoma, and it is almost always manifest at the time of delivery and then fails to regress spontaneously after delivery. The implications of these observations are that women diagnosed with metastatic melanoma during pregnancy need not abort their fetus out of a fear of transplacental spread, and active therapy for a fetus born in the setting of placental metastases is not warranted.

7. Is the termination of pregnancy associated with the regression of melanoma?

Although there have been anecdotal reports of nevi that enlarged and regressed during a previous pregnancy, in patients who later had metastatic melanoma, this is apparently an unusual event. There are anecdotal reports of postpartum spontaneous regression of melanoma in an affected woman,[48,49] but this has been observed infrequently and has not been documented in most studies.[14,36,50] A

strong consensus now exists that survival is not adversely affected by pregnancy. There are no studies to suggest that therapeutic abortion or induced delivery will induce tumor regression in the mother. In fact, it has been noted in a series of Russian women that patients who underwent abortion actually did worse.[51] Thus, there is no rationale for altering the course of pregnancy itself as a therapeutic intervention for a woman's melanoma.

8. Should women who previously were diagnosed with melanoma avoid pregnancy?

The issue here is whether pregnancy activates micrometastatic disease. There is no convincing evidence that pregnancy activates or stimulates dormant micrometastatic disease, although anecdotal case reports certainly suggest that this may happen in some cases. One of the difficulties in addressing this question is that it is impossible to know prospectively which patients are harboring micrometastases. One author noted similar five- and ten-year survival rates for 115 patients who were pregnant with melanoma compared with 330 female melanoma patients who were never pregnant during or after their diagnosis.[23] The pregnant group, however, had a higher frequency of lymph node involvement at the time of diagnosis. A better survival was actually noted for 71 patients who were pregnant within a year before or five years after a diagnosis of melanoma, but the control group consisted of only 31 women who did not get pregnant during a similar interval and who actually had higher stage disease.[47] In another study, women diagnosed with melanoma before getting pregnant were compared with women diagnosed after completing all pregnancies.[39] The latter group actually appeared to do worse at five years, although statistical comparison was not provided. In a retrospective study conducted at Duke University, 43 women with stage I melanoma who became pregnant within the next five years had prognoses similar to those of 337 women who did not get pregnant, both in terms of relapse and disease-free survival.[9]

There is no evidence that nulliparous women as a group differ from parous women as a group, in terms of prognosis from the time of a subsequent diagnosis of melanoma while pregnant. In a study that compared 85 women diagnosed with melanoma before their first pregnancy with 143 women who had completed all pregnancies, melanoma developed in 68 between pregnancies and in 92 during pregnancy, and there was no difference in these groups.[39] Two other small studies also found no difference in prognosis for nulliparous as opposed to parous women,[48,52] although the studies were small in scope. The only trials that address the issue of the importance of subsequent pregnancy on prognosis have failed to identify parity as an important variable in multivariate analysis.[39] In the absence of definitive data, many authorities have recommended that women avoid pregnancy for two to five years after a diagnosis of melanoma, mainly because that is the time period during which most recurrences are diagnosed.[19,41,49] In one study, such patients who did become pregnant were actually used as controls to compare with patients who were being diagnosed with melanoma for the first time while pregnant.[37]

9. Should women who previously were diagnosed with melanoma during a pregnancy avoid subsequent pregnancy?

Historically, there has been great concern regarding the risk of subsequent pregnancy in women who were initially diagnosed with melanoma during a previous pregnancy, based on the presumption that these melanomas in particular may be influenced adversely by growth factors and hormones secreted during pregnancy. Earlier observers felt strongly that pregnancy worsened the prognosis in this group of patients.[25,49] There is no objective evidence that this group is at higher risk with subsequent pregnancy, however. Despite this, the consensus is to recommend the deferral of subsequent pregnancy for two to three years in women in whom a primary melanoma developed during pregnancy.[7,13,25,32]

10. Do physicians who care for pregnant women fail to diagnose melanoma during pregnancy?

Although anecdotal reports suggest that physicians fail to diagnose melanoma during pregnancy, there are no objective data to verify this concern. It is not uncommon, however, to attribute many complaints or physical changes to pregnancy that might be evaluated differently were a patient not pregnant. Whereas pregnancy may induce darkened pigmentation in nevi and lead patients to become more aware of their nevi, physicians must maintain the same index of suspicion for melanoma as they would in the general population. National cancer authorities currently emphasize the A, B, C, D danger signs of melanoma: *A*symmetry, *B*orderline irregularity, *C*olor variations from one area to another, and *D*iameter larger than 6 mm.[5] Because of the long-standing literature suggesting an association between melanoma and pregnancy and the dire implications of subsequent metastatic melanoma in a woman with young children, physicians should be extremely cautious in discounting observations of changing nevi in pregnant patients. As noted earlier, the standard of care is that a biopsy is warranted if there are any suspicious features noted in a pigmented cutaneous lesion during pregnancy.

Conclusion

In summary, clinical observations strongly suggest that some women may have melanoma whose biologic behavior is influenced adversely by pregnancy. In a woman who has never had melanoma, concern about the possible effects or future risk of melanoma should have no influence on her desire to get pregnant. There is no reason to terminate pregnancy because of fear of metastases to the fetus or in hopes that it will alter the course of the melanoma in the mother. In a woman previously diagnosed with melanoma, whether nulliparous or parous, there are no data to recommend an abortion in the belief that pregnancy has activated micrometastatic disease and that abortion will reverse this process. The management of

melanoma and the prognosis are based on the stage at the time of diagnosis. Because several studies have suggested that pregnant women diagnosed with melanoma are more likely to have deeper lesions (either because of delays in diagnosis or hormonal or growth factor stimulation), physicians caring for pregnant women must be especially alert to the potential of melanoma and not routinely dismiss changes in nevi as being secondary effects of pregnancy. For patients with deeper melanomas, who are at high risk of recurrence, most of which take place within two to three years of diagnosis, many have recommended that they be advised of this and perhaps defer pregnancy until after two to three years of disease-free survival.

REFERENCES

1. Glass AG, Hoover RN: The emerging epidemic of melanoma and squamous cell skin cancer. JAMA 1989; 262:2097-2100

2. Rifkin RM, Thomas MR, Mughal TI, Kaur JS, Krebs LU, Robinson WA: Malignant melanoma—Profile of an epidemic. West J Med 1988; 149:43-46

3. Boring CC, Squires TS, Tong T, Montgomery BA: Cancer statistics, 1994. Ca Cancer J Clin 1994; 44:7-26

4. Miller BA, Ries LAG, Hankey BF, Kosary CL, Edwards BK (Eds): Cancer Statistics Review: 1973-1989, National Cancer Institute publication No. (NIH) 92-2789, 1992

5. Koh HK: Cutaneous melanoma. N Engl J Med 1991; 325:171-182

6. NIH Consensus Conference: Diagnosis and treatment of early melanoma. JAMA 1992; 268:1314-1319

7. Colbourn DS, Nathanson L, Belilos E: Pregnancy and malignant melanoma. Semin Oncol 1989; 16:377-387

8. Driscoll MS, Grin-Jorgensen CM, Grant-Kels JM: Does pregnancy influence the prognosis of malignant melanoma? J Am Acad Dermatol 1993; 29: 619-630

9. Slingluff CL Jr, Seigler HF: Malignant melanoma and pregnancy. Ann Plastic Surg 1992; 28:95-99

10. Jatoi I, Gore ME: Sex, pregnancy, hormones, and melanoma. BMJ 1993; 307:2-3

11. Garge C: Pregnancy, hormone preparations and malignant melanoma. Hautarzt 1993; 44:347-352

12. Slingluff CL Jr, Reintgen D: Malignant melanoma and the prognostic implications of pregnancy, oral contraceptives, and exogenous hormones. Semin Surg Oncol 1993; 9:228-231

13. Kjems E, Krag C: Melanoma and pregnancy—A review. Acta Oncol 1993; 32:371-378

14. Smith RS, Randall P: Melanoma during pregnancy. Obstet Gynecol 1969; 34:825-829

15. Barber HRK: Malignant disease in the pregnant woman, *In* Coppelson M (Ed): Gynecologic Oncologic: Fundamental Principles and Clinical Practice. New York, NY, Churchill Livingstone, 1981, pp 795-806

16. Potter JF, Schoeneman M: Metastasis of maternal cancer to the placenta and fetus. Cancer 1970; 25:380-387

17. Ariel IM: Theories regarding the cause of malignant melanoma. Surg Gynecol Obstet 1980; 150:907-917

18. Donegan WL: Cancer and pregnancy. Ca Cancer J Clin 1983; 33: 194-214

19. Holly EA, Weiss NS, Liff JM: Cutaneous melanoma in relation to exogenous hormones and reproductive factors. J Natl Cancer Inst 1983; 70:827-831

20. Holman CDJ, Armstrong BK, Heenan PJ: Cutaneous malignant melanoma in women: Exogenous sex hormones and reproductive factors. Br J Cancer 1984; 50:673-680

21. Gallagher RP, Elwood JM, Hill GB, Coldman AJ, Threlfall WJ, Spinelli JJ: Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada Melanoma Study. Br J Cancer 1985; 52:901-907

22. Green A, Bain C: Hormonal factors and melanoma in women. Med J Aust 1985; 142:446-448

23. Osterlind A: Malignant melanoma in Denmark—Occurrence and risk factors. Acta Oncol 1990; 29:833-854

24. Zanetti R, Franceschi S, Rosso S, Bidoli E, Colonna S: Cutaneous malignant melanoma in females: The role of hormonal and reproductive factors. Int J Epidemiol 1990; 19:522-526

25. Pack GT, Scharnagel IM: The prognosis for malignant melanoma in the pregnant woman. Cancer 1951; 4:324-334

26. Sadoff L, Winkley J, Tyson S: Is malignant melanoma an endocrine-dependent tumor? Oncology 1973; 27:244-257

27. Cochran AJ, Todd G, Hart DM, Morrison LJA, MacKie RM: Reaction of the leukocytes of melanoma patients and control donors, including pregnant women, with melanoma and fetus-derived materials. Cancer Immunol Immunother 1982; 14:78-81

28. Houghton AN, Flannery J, Viola MV: Malignant melanoma of the skin occurring during pregnancy. Cancer 1981; 48:407-410

29. George PA, Fortner JG, Pack GT: Melanoma with pregnancy. Cancer 1960; 13:854-859

30. Eldh J, Boeryd B, Peterson LE: Prognostic factors in cutaneous malignant melanoma in stage I—A clinical, morphological and multivariate analysis. Scand J Plast Reconstr Surg 1978; 12:243-255

31. Winton GB, Lewis CW: Dermatoses of pregnancy. J Am Acad Dermatol 1982; 6:977-998

32. Hersey P, Morgan G, Stone DE, et al: Previous pregnancy as a protective factor against death from melanoma. Lancet 1977; 1:451-452

33. Bork K, Bräuninger W: Prior pregnancy and melanoma survival (Letter). Arch Dermatol 1986; 122:1097

34. Elwood JM, Coldman AJ: Previous pregnancy and melanoma prognosis (Letter). Lancet 1978; 2:1000-1001

35. Lederman JS, Sober AJ: Effect of prior pregnancy on melanoma survival (Letter). Arch Dermatol 1985; 121:716

36. Shiu MH, Schottenfeld D, Maclean B, et al: Adverse effect of pregnancy on melanoma. Cancer 1976; 37:181-187

37. Sutherland CM, Loutfi A, Mather FJ, Carter RD, Krementz ET: Effects of pregnancy upon malignant melanoma. Surg Gynecol Obstet 1983; 157: 443-446

38. Holly EA: Melanoma and pregnancy. Recent Results Cancer Res 1986; 102:118-126

39. MacKie RM, Bufalino R, Morabito A, Sutherland C, Cascinelli N: Lack of effect of pregnancy on outcome of melanoma—The World Health Organisation Melanoma Programme. Lancet 1991; 337:653-655

40. Reintgen DS, McCarty KS Jr, Vollmer R, Cox E, Seigler HF: Malignant melanoma and pregnancy. Cancer 1985; 55:1340-1344

41. Slingluff CL Jr, Reintgen DS, Vollmer RT, Seigler HF: Malignant melanoma arising during pregnancy—A study of 100 patients. Ann Surg 1990; 211:552-559

42. Wong DJ, Strassner HT: Melanoma in pregnancy. Clin Obstet Gynecol 1990; 33:782-791

43. Johnson TM, Smith JW II, Nelson BR, Chang A: Current therapy for cutaneous melanoma. J Am Acad Dermatol 1995; 32:689-707

44. McNeer G: The clinical behavior and management of malignant melanoma. JAMA 1961; 176:85-88

45. Anderson JF, Kent S, Machin GA: Maternal malignant melanoma with placental metastasis: A case report with literature review. Pediatr Pathol 1989; 9:35-42

46. Rothman LA, Cohen CJ, Astarloa J: Placental and fetal involvement by maternal malignancy: A report of rectal carcinoma and review of the literature. Am J Obstet Gynecol 1973; 116:1023-1034

47. White LP, Linden G, Breslow L, et al: Studies on melanoma—The effect of pregnancy on survival in human melanoma. JAMA 1961; 177:51-54

48. Rampen FH, Mulder JH: Malignant melanoma: An androgen-dependent tumor? Lancet 1980; 1:562-564

49. Byrd BF, McGanity WF: The effect of pregnancy on the clinical course of melanoma. South Med J 1954; 47:196-200

50. Nathanson L, Hall TC, Farber S: Biological aspects of human malignant melanoma. Cancer 1967; 20:650-655

51. Trapeznikov NN, Khasanov ShR, Iavorskiĭ VV: [Skin melanoma and pregnancy.] Vopr Onkol 1987; 33:40-46 [Engl Abstr]

52. Shaw HM, Milton GW, Farago G, McCarthy WH: Endocrine influences on survival from malignant melanoma. Cancer 1978; 42:669-677

Epitomes

Important Advances in Clinical Medicine

General Surgery

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association, and the summaries were prepared under the direction of Theodore R. Schrock, MD, and the panel.

Pregnancy-Associated Breast Cancer

THE TERM PREGNANCY-ASSOCIATED breast cancer refers to a breast cancer that has grown with exposure to the hormonal milieu of pregnancy. A breast cancer diagnosed in a pregnant woman is a pregnancy-associated breast cancer, a situation reported in as many as 1 in 3,000 pregnancies. Pregnancy-associated breast cancer also includes breast cancers diagnosed in the postpartum period because the preclinical growth phase for breast cancers lasts many months or even years. A breast cancer diagnosed within a year after the completion of pregnancy almost certainly existed in the breast while the woman was pregnant and hence may also be considered to be a pregnancy-associated breast cancer.

Pregnancy-associated breast cancer has been recognized with increasing frequency in recent decades. It occurs in between 10% and 25% of breast cancer patients younger than 35 years. This increase in the incidence of pregnancy-associated breast cancer may be related to more women delaying childbirth into their 30s and 40s when breast cancer more commonly occurs.

Breast cancer associated with pregnancy has been reported to portend an extremely poor outcome. Early studies suggested that the prognosis of this cancer is dismal, with five-year survival rates being less than 20%. Recent studies, however, have found no difference in survival, stage for stage, between pregnancy-associated and non–pregnancy-associated breast cancer.

A consensus does not exist as to whether pregnancy-associated breast cancer represents a biologically more aggressive malignant process than does that not associated with pregnancy, primarily because it is a challenging disease to study. The problem in analyzing survival following this cancer is in the identification of appropriate control groups. Because pregnancy-associated breast cancer is uncommon, most studies have first found a group of patients with this form of breast cancer and then attempted to identify a matched control group for statistical comparison. This process introduces a possible selection bias that is decreased if the two groups are identified concomitantly by the same selection criteria.

A recent study showed that women 30 years of age or younger with pregnancy-associated breast cancer had decreased rates of overall survival and disease-free survival compared with similar women whose breast cancer was not associated with pregnancy. This difference in survival appeared to be a stage-related phenomenon because women with pregnancy-associated breast cancer were more likely to have larger and more advanced cancers at the time of a definitive operation.

The design of the study limits generalizations regarding comparative tumor behavior in pregnancy-associated and non–pregnancy-associated breast cancer, but it appears that early-stage breast cancer has a similar prognosis whether or not it is associated with pregnancy. By contrast, advanced pregnancy-associated breast cancer appears to have a worsened prognosis than does non–pregnancy-associated breast cancer. The difference may relate in part to the extent of nodal spread, which in these patients tended to be greater than with non–pregnancy-associated cancer.

Unlike tumor pathogenesis and nodal metastases, tumor size is a variable that is subject to clinical detection. Clinical detection can be impaired by physiologic engorgement of the breasts during pregnancy and lactation. Breast ultrasonography can be useful in this regard because it can distinguish and characterize masses within a gravid or lactating breast and can be used to guide core-needle biopsy for cytologic or histologic diagnosis.

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REFERENCES

Anderson BO, Petrek JA, Byrd DR, Senie RT, Borgen PI: Pregnancy influences breast cancer stage at diagnosis in women 30 years of age and younger. Ann Surg Oncol 1996 March, in press

Anderson BO, Senie RT, Vetto JT, Wong GV, McCormick B, Borgen PI: Improved survival in young women with breast cancer. Ann Surg Oncol 1995; 2:407-415

Petrek JA: Breast cancer and pregnancy. J Natl Cancer Inst Monogr 1994; 16:113-121

Schoultz E, Johansson H, Wilking N, Rutqvist LE: Influence of prior and subsequent pregnancy on breast cancer prognosis. J Clin Oncol 1995; 13:430-434

Laparoscopic Operation for Treatment of Gastroesophageal Reflux

HEARTBURN AND OTHER symptoms of reflux affect more than 20 million adult Americans. Medical therapy is relatively effective in the acute phase of the disease, but fails to alter its natural history, particularly the tendency to relapse. Recurrent or persistent reflux can seriously damage the esophagus, causing strictures, the development of Barrett's ulcer, and other complications. Thus, the surgical correction of reflux is indicated in patients whose symptoms fail to resolve while they are receiving medical therapy or in those in whom symptoms recur. An operation permanently restores the competency of the cardia in about 90% of patients; nevertheless, gastroenterologists and occasionally patients themselves were heretofore reluctant to proceed with it, mainly because of the pain, discomfort, and risks associated with the operation and its recovery.

Laparoscopic techniques now offer a new alternative. Laparoscopic Nissen fundoplication can be done with relative safety and with good immediate results. When performed by surgeons with experience in the management of esophageal disease and in laparoscopy, this approach yields results that are comparable to those done by the open approach. Indeed, most studies comparing the outcome of patients operated on by the open and laparoscopic approaches show a lower need for analgesics and fewer complications in the patients when done with minimally invasive techniques.

As experience is accumulating, several elements are becoming clear. First, the procedure demands a level of competency in laparoscopy that far exceeds that needed to do a cholecystectomy. Thus, adequate training is paramount, and appropriate supervision and assistance by a qualified surgeon are imperative during the learning period. Second, there is a tendency on the part of patients, as well as some members of the medical profession, to regard the laparoscopic antireflux operation as a relatively minor procedure. Surgeons must carefully guard against this erroneous assumption: the indication for antireflux surgical intervention remains the same. Third, obesity makes the operation particularly difficult, and the increased intraabdominal pressure caused by it may contribute to the development of a postoperative hiatal hernia. Thus, every effort should be made to ensure that an obese patient loses weight before the operation. Last, to perform a good operation, the surgeon must have substantial information about the pathophysiology of the disease and the degree to which the patient is affected. It is not simply a matter of "diagnosis," but one of characterizing and identifying associated problems. Thus, all patients should have a complete workup before the operation. That means, for the average patient, esophageal function testing with manometry and 24-hour pH monitoring and endoscopy with biopsy. Upper gastrointestinal series are helpful because they provide valuable information about the relations of the lower esophagus to adjacent structures.

Reoperations in this area are difficult and the results far inferior to those obtained the first time around. To avoid them, the surgeon must know the extent to which the disease affects the patient, tailor the operation to the patient's needs, and perform the procedure flawlessly.

Based on an experience gathered over the past five years, we think that this approach offers a new and superior alternative to patients with reflux refractory to medical therapy. In essence, it provides the same time-proven, effective operation to restore the competency of the cardia, with less discomfort and faster return to a normal life.

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REFERENCES

Collard JM, de Gheldere CA, De Kock M, Otte JB, Kestens PJ: Laparoscopic antireflux surgery—What is real progress? Ann Surg 1994; 220:146-154

Hinder RA, Filipi CJ, Wetscher G, Neary P, DeMeester TR, Perdikis G: Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease. Ann Surg 1994; 220:472-483

Peters JH, Heimbucher J, Kauer WKH, Incarbone R, Bremner CG, DeMeester TR: Clinical and physiologic comparison of laparoscopic and open Nissen fundoplication. J Am Coll Surg 1995; 180:385-393

Weerts JM, Dallemagne B, Hamoir E, et al: Laparoscopic Nissen fundoplication: Detailed analysis of 132 patients. Surg Laparosc Endosc 1993; 3:359-364

Laparoscopic Sonography and Staging of Liver Cancer

ULTRASONOGRAPHY DONE at open operation aids the surgeon in detecting and sampling unsuspected liver metastases and guides hepatic resection or ablative treatment such as cryotherapy. Laparoscopic ultrasonography is readily performed and adds materially to the conduct of laparoscopic staging operations aimed at preventing futile laparotomy.

Laparoscopic ultrasound devices usually consist of linear-array transducers operating at frequencies of 6 to 10 MHz mounted on rigid or flexible 10- to 12-mm diameter probes. Flexible probes with transducers operating in the range of 6 to 7.5 MHz are best suited for visualizing the liver. Rigid probes are best suited for doing ultrasound-directed biopsy during which the biopsy needle must be parallel with the longitudinal axis of the transducer. Newer probes that allow the passage of a core or aspirating needle by a needle guide aligned parallel with the beam of the ultrasound waves may minimize the double-fulcrum effect encountered with laparoscopic freehand biopsy.

Patients with primary liver cancer have been shown to benefit from laparoscopic staging. Most will be found incurable by traditional resection because of multifocal disease, peritoneal carcinomatosis, or severe cirrhosis. Most hepatic tumors in western practice are secondary, and many derive from colon or rectal primary tumors. Complete resection or destruction by other means may result in prolonged survival rates in 25% to 35% of a selected group of such patients. Most hepatic resections and cryoablations require laparotomy. The laparoscopic determination of incurability rather than determination at laparotomy results in less morbidity, cost, and time in the hospital.

The technique of the laparoscopic assessment of the liver consists of placing an umbilical and a right-sided

cannula. Examination begins with the telescope in the umbilical port and then the right-sided port. If no visual sign of incurability is found, the ultrasound probe is passed through the right-sided port. Laparoscopic ultrasonography consists of obtaining systematic views from both the anterior and posterior surfaces. The instruments may be switched between ports, or an additional left-sided port may be placed for detailed examination of the left lateral segment. If adhesions from previous operations preclude easy access to the lateral segment, most of this structure can be viewed ultrasonographically by placing the transducer against the falciform ligament and rotating the transducer to view obliquely through the lateral segment.

Ultrasonography of the liver done at laparotomy may detect an additional 10% to 40% of tumor deposits not visualized by conventional preoperative imaging methods or not palpable by a surgeon. The addition of hepatic computed tomographic arterial portography improves the accurate determination of the extent of hepatic tumor preoperatively; however, this method may overestimate the extent of extrahepatic or hepatic tumor in more than 10% of cases. Laparoscopic ultrasonography in one study defined hepatic tumors that were not visible by laparoscopy in a third of patients. With the use of laparoscopic ultrasonography only, 16% of patients were found to have disease that was not curable by conventional hepatic resection. Our experience suggests that the addition of laparoscopic ultrasonography to laparoscopy for the staging of primary and secondary hepatic tumors defines an additional 15% to 20% of patients to be incurable by treatment with either hepatic resection, cryoablation, or a combination of both. Patients found incurable by laparoscopic methods are generally returned home the same day.

Should the laparoscopic staging operation be done synchronously with laparotomy or as a separate procedure? The former approach is desirable in centers with competence in hepatic surgical procedures that are prepared to proceed with definitive treatment in the same setting. The latter is appropriate for surgeons who may refer cases on after determining possible curability.

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REFERENCES

Goletti O, Buccianti P, Cavina E: Laparoscopic sonography: Basics and equipment. *In* Laparoscopic Sonography. Pisa, Italy, Editoriale Grasso, 1994, pp 11-31

John T, Greig J, Crosbie J, Miles WFA, Garden JO: Superior staging of liver tumors with laparoscopy and laparoscopic ultrasound. Ann Surg 1994; 220:711-719

Karl RC, Morse SS, Halpert RD, Clark RA: Preoperative evaluation of patients for liver resection—Appropriate CT imaging. Ann Surg 1993; 217:226-232

Machi J, Sigel B, Zaren HA, Kurohiji T, Yamashita Y: Operative ultrasonography during hepatobiliary and pancreatic surgery. World J Surg 1993; 17:640-646

Biomarkers for Breast Cancer

BIOMARKERS ARE most helpful in the management of breast cancer in its earliest stages—that is, node-negative breast cancer—when we must identify patients who are at the lowest or highest risk for recurrent or metastatic disease with early mortality. Apart from lymph node status (N), tumor size (T), and grade (G), the only breast cancer markers having proven clinical usefulness are estrogen receptor (ER), progesterone receptor (PR), and S-phase fraction (SPF). With these six well-established prognostic variables, clinicians still treat virtually all patients with stage I or stage II breast cancer with parenteral adjuvant therapy. This treatment for all is necessary to reduce the chance of metastases in those few patients—20% to 50%—who are truly at risk. Thus, there remains considerable incentive to discover new prognostic markers that will identify the few persons at risk, thereby sparing the majority who do not need parenteral adjuvant therapy. As well, biomarkers would be helpful in identifying patients less likely to respond to conventional chemotherapy or hormonal therapy.

Despite great interest and intense searching, there is no ideal prognostic indicator under development or on the horizon. Nor is there a suitable combination of markers that, for any given patient, can predict the natural course of the disease. Increasing optimism that a measure of breast tumor angiogenesis (microvessel density as detected by factor VIII staining) can at least discriminate between high- and low-risk, node-negative patients has now been muted by a recent large clinical study demonstrating the assay's unacceptable variability and failure to predict patients' outcome.

Critical among the established guidelines for the clinical development of any new prognostic marker is that the marker have biologic relevance to the disease process. In this regard, all measures of tumor angiogenesis remain on sound footing. Just as the best use of the estrogen receptor is to select patients for antiestrogen therapy, the ultimate clinical usefulness of a biomarker for microvessel density might be its ability to select candidates for antiangiogenesis therapy. Such is the emerging promise of other previously touted breast cancer prognostics, including the oncogenes c-*erb* B-2 (HER-2/*neu*) and p53. Gene therapies designed to correct mutations in the p53 tumor-suppressor gene have now entered clinical trials. Likewise, various therapeutic approaches are being developed to target the 25% of breast cancers that overexpress the c-*erb* B-2 oncogene; one approach, in particular, uses a tumor-inhibiting anti-HER-2 monoclonal antibody that in phase II studies produced complete and partial clinical responses without substantial toxicity in patients refractory to conventional breast cancer chemotherapy. These examples should help reinforce our interest in and continued search for new biomarkers that will serve as targets for the development of novel therapeutic agents, even if they fail to live up to our expectations as breast cancer prognostic factors.

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REFERENCES

Axelsson K, Ljung BM, Moore DH II, et al: Tumor angiogenesis as a prognostic assay for invasive ductal breast carcinoma. J Natl Cancer Inst 1995; 87:997-1008

Benz CC, Brandt BH, Zanker KS: Gene diagnostics provide new insights into breast cancer prognosis and therapy. Gene 1995; 159:3-7

Gasparini G, Pozza F, Harris AL: Evaluating the potential usefulness of new prognostic and predictive indicators in node-negative breast cancer patients. J Natl Cancer Inst 1993; 85:1206-1219 (165 refs)

Levine MN, Browman GP, Gent M, Roberts R, Goodyear M: When is a prognostic factor useful?—A guide for the perplexed. J Clin Oncol 1991; 9:348-356

McGuire WL: Breast cancer prognostic factors: Evaluation guidelines (Editorial). J Natl Cancer Inst 1991; 83:154-155

Liver Transplantation—Treatment Option for Selected Liver Tumors

SURGICAL RESECTION for primary liver cancer, mainly hepatocellular carcinoma, remains the only treatment proved capable of cure. Many patients cannot undergo partial resection, however, because of decreased liver function due to either cirrhosis or a centrally located tumor. For these patients, total hepatic resection followed by liver transplantation offers an alternative. It was this type of patient that became the first long-term survivor after liver transplantation: a 19-month-old girl with an unresectable hepatoma. She had a transplantation in 1967 and, unfortunately, died of recurrent hepatoma 14 months after the operation. In 1983 the National Institutes of Health Consensus Conference on liver transplantation stated that liver transplantation was no longer an experimental therapy, thereby proliferating the number of liver transplant centers in the United States. Primary hepatic carcinoma not amenable to resection was one of the indications for transplantation. Total hepatic resection and liver transplantation allowed a wider resection margin and would hopefully result in an improved cure rate. Unfortunately, like the little girl in 1967, many patients who survived the liver transplantation later died of recurrent cancer. Thus, many liver transplant centers consider a primary hepatic malignancy a contraindication to liver transplantation, even if the tumor is totally confined to the liver.

Some centers have continued to perform liver transplantation in these patients, however. The survival rate after liver transplantation in patients with liver cancer had been approximately 25% at three years, yet more recent reports in similar patient populations have described three-year survival rates of 46% to 66%. The reasons for the improved results are not clear, but they are probably due to at least three factors: improved surgical technique, more refined patient selection criteria, and the availability of combined modality therapy.

Advances and refinements in the surgical technique of liver transplantation and postoperative management have led to an overall improvement in patient survival. The expected one-year survival rate in liver transplant patients with benign diseases was 60% to 70% and is now 80% to 90%.

We have refined our patient selection criteria. Any patient with an extrahepatic tumor, including lymph node metastases, has an extremely poor prognosis and should not undergo either partial resection or total resection with liver transplantation. No other factors have been shown to reliably predict failure, but other preoperative characteristics that have demonstrated increased relative risk of tumor recurrence—in some but not all clinical series—are tumor size greater than 5 cm, bilobar involvement, and macroscopic vascular invasion. It is difficult to decide which risk factors should be "relative" and which "absolute" contraindications to total resection with liver transplantation. Our center excludes patients with portal vein invasion, but does consider patients with tumors larger than 5 cm or bilobar involvement.

Finally, centers are now treating patients with combined modality therapy. All the recent reports describing clinical series of patients undergoing liver transplantation for primary liver cancer use either adjuvant or neoadjuvant therapy in their treatment plan. The implementation of chemotherapy has been the only notable therapeutic change when compared with historical controls. At this time, no randomized, prospective, controlled trials have been done to determine the effectiveness of radiation therapy or adjuvant or neoadjuvant chemotherapy in these patients. Our center currently uses neoadjuvant fluorouracil and chemoembolization with doxorubicin hydrochloride, as well as postoperative adjuvant chemotherapy with doxorubicin and fluorouracil for four months.

The possible liver transplant recipients far outnumber the possible donors. This mismatch between supply and demand creates difficulty in allocating organs. The use of donor livers in patients with liver tumors will shift organs away from patients with benign liver diseases, who have a better predicted long-term survival. Therefore, even though there is some evidence that liver transplantation is superior to partial resection in certain patients with small tumors and cirrhosis, most centers recommend partial resection (if feasible) in these patients, to conserve the availability of donor livers.

Patients with chronic hepatitis should be screened for the presence of liver cancer. Early referral before the cancer spreads outside the liver will increase the number of patients who can be effectively treated. Because the organ supply is limited, patients with cirrhosis who can tolerate a partial resection should have it. In cases where the tumor cannot be removed with a partial liver resection, total liver resection with liver transplantation is the only proven curative alternative. While a patient is waiting for a donor liver, which may be six months or longer, our center uses chemoembolization and neoadjuvant chemotherapy to control disease. Multicenter trials are under way to evaluate the effectiveness of adjuvant chemotherapy in these patients. These trials should provide necessary information as to the best combination of surgical therapy and chemotherapy in the management of liver tumor cases.

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REFERENCES

Olthoff KM, Rosove MH, Shackleton CR, et al: Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. Ann Surg 1995; 221:734-743

Schwartz ME, Sung M, Mor E, et al: A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg 1995; 180:596-603

Tan KC, Rela M, Ryder SD, et al: Experience of orthotopic liver transplantation and hepatic resection for hepatocellular carcinoma of less than 8 cm in patients with cirrhosis. Br J Surg 1995; 82:253-256

Skin-Sparing Mastectomy With Immediate Tissue Reconstruction

BREAST CANCER is frequently treated with breast-conserving techniques, including lumpectomy, axillary dissection, and radiation therapy. Mastectomy with lymph node dissection remains the treatment of choice in many patients, however. To facilitate patient acceptance of this recommendation, skin-sparing mastectomy and immediate transverse rectus abdominis myocutaneous (TRAM) flap reconstruction were developed in 1991. This procedure satisfies oncologic requirements and provides superior reconstructive results compared with conventional techniques.

The proper surgical treatment of breast cancer requires the removal of the nipple-areolar complex and previous biopsy scars in the process of mastectomy. Previously an elliptical incision was designed to satisfy these criteria. This provided for a straight-line closure when no reconstruction was done but produced a distinctly patchwork appearance when immediate tissue reconstruction was performed. Because patients increasingly seek immediate reconstruction and express a greater preference for reconstruction with their own tissue, newer methods were sought that would improve the results while maintaining strict oncologic standards.

Of note, several reviews have determined that immediate myocutaneous flap breast reconstruction results in no significant differences in patient survival and in the detection of recurrences when compared with mastectomy alone. Patients may also undergo radiation therapy if necessary after this type of reconstruction.

Technically, skin-sparing mastectomy involves the same-thickness skin flaps as in a conventional modified radical mastectomy but is performed through a limited incision that is dictated by the position of previous biopsy scars. The natural inframammary crease is preserved. Axillary dissection may be done through a separate transaxillary incision. The result is a completed mastectomy with all breast tissue removed and an empty breast skin envelope. The removed skin is then replaced with abdominal skin. The remaining skin is removed from the TRAM flap, which is placed in the breast envelope as a living implant. The flap therefore settles into the breast's natural contour, resulting in a superior aesthetic shape that closely resembles the natural breast.

From 1993 to the present, we have performed skin-sparing mastectomies with TRAM flap reconstruction on 31 patients at the University of Washington Medical Center (Seattle). We select patients for immediate reconstruction who are unlikely to require irradiation and who are anticipated to have fewer than three positive lymph nodes. Of the 31 patients, 5 underwent bilateral skin-sparing procedures. Of the total of 36 TRAM flaps thus performed, 12 were transferred microsurgically as free TRAM flaps and 24 by standard pedicled techniques. All flaps healed without serious complications, and no patients sustained delays in further treatment because of problems related to their reconstructions.

Skin-sparing mastectomy with immediate autogenous reconstruction provides superior results to traditional techniques and improved patient satisfaction while maintaining all appropriate oncologic principles for surgical resection. This provides an excellent treatment of patients when breast-conserving techniques are not applicable. This technique is not appropriate when the immediate reconstruction is performed with implants and should not be applied when the mastectomy is done for recurrence in an irradiated breast following unsuccessful breast-conserving therapy.

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REFERENCES

Elliott LF, Eskenazi L, Beegle PH, Podres PE, Drazan L: Immediate TRAM flap breast reconstruction: 128 consecutive cases. Plast Reconstr Surg 1993; 92:217-227

Hartrampf CR, Scheflan M, Black PW: Breast reconstruction with a transverse abdominal island flap. Plast Reconstr Surg 1982; 69:216-225

Johnson CH, van Heerden JA, Donohue JH, Martin JK Jr, Jackson IT, Ilstrup DM: Oncological aspects of immediate breast reconstruction following mastectomy for malignancy. Arch Surg 1989; 124:819-823

Schain WS, Wellisch DK, Pasnau RO, Landsverk J: The sooner the better: A study of psychological factors in women undergoing immediate versus delayed breast reconstruction. Am J Psychiatry 1985; 142:40-46

Slavin SA, Love SM, Goldwyn RM: Recurrent breast cancer following immediate reconstruction with myocutaneous flaps. Plast Reconstr Surg 1994; 93:1191-1204

Toth BA, Lappert P: Modified skin incisions for mastectomy: The need for plastic surgical input in preoperative planning. Plast Reconstr Surg 1991; 87:1048-1053

Thromboembolism Prophylaxis in Surgical Patients

VENOUS THROMBOEMBOLISM continues to be a major cause of morbidity and mortality in surgical patients and those who have survived severe injury. Deep venous thrombosis (DVT) occurs in 19% to 25% of patients being treated surgically and in more than 50% of trauma patients. Currently symptomatic pulmonary embolism develops in 1% to 2% of trauma patients and, of these, 25% to 50% die. Those at highest risk of thromboembolism are patients undergoing major thoracic or abdominal operations; those suffering fractures of the spine, pelvis, or lower extremities; or patients older than 30 years. Because of the common occurrence of thromboembolic complications in surgical patients, it is important that surgeons have an effective approach to their prevention.

Available methods of thromboembolism prophylaxis include pharmacologic (heparin), mechanical (sequential compression devices and foot pumps), and surgical (caval filters). Heparin therapy is currently the standard. Both the mechanical and the surgical methods of prophylaxis are used when heparin therapy is contraindicated or has failed.

Several heparin regimens are used widely: low-dose heparin (5,000 units administered subcutaneously twice or three times a day), adjusted-dose heparin (enough to raise the partial thromboplastin time [aPTT] 5 seconds

above normal), and unmonitored low-molecular-weight heparin (30 mg given subcutaneously twice per day).

Both unfractionated (standard) and low-molecular-weight heparin exert their anticoagulant effect through the potentiation of antithrombin III. Therefore, for any heparin regimen to be effective in preventing thrombosis, the patient must have adequate antithrombin III levels. We and others have recently shown that the majority of severely injured patients have antithrombin III levels that are substantially depressed. Therefore, the patients at highest risk for thromboembolism have low antithrombin III levels.

In the past decade, the approach of progressively adjusting the heparin dose to maintain the aPTT above normal (adjusted-dose heparin) has been shown to be superior to the low-dose approach in preventing venous thromboembolism. Adjusting the heparin dose compensates for the depleted antithrombin III levels. An important note is that the increased doses of heparin used with this method have not been shown to result in more or worse bleeding complications.

A new group of heparin products, low-molecular-weight heparins, has recently captured great interest. These are standard heparins that have been subjected to a fractionation process to yield a purer compound with a higher concentration of the subunit responsible for the potentiation of antithrombin III. The important differences between standard and low-molecular-weight heparins are that low-molecular-weight heparins have a longer half-life, a more dependable absorption, a more potent effect on antithrombin III, and may be less likely to incite heparin-induced thrombocytopenia. Despite these possible advantages, a considerable disadvantage of the low-molecular-weight heparins is that most laboratories are unable to monitor their anticoagulant effect. As with standard heparin, low-molecular-weight heparin in the absence of adequate antithrombin III is doomed to fail at preventing thromboembolism.

Several low-molecular-weight heparins are available in Canada, and now there are two in the United States. These products are protected by patents, and so their manufacturers have an interest in sponsoring research to promote them. But the majority of current low-molecular-weight heparin efficacy trials have compared the use of low-molecular-weight heparin with that of placebo and low-dose heparin rather than with adjusted-dose heparin. The trials that have compared the use of low-molecular-weight heparin with that of adjusted-dose heparin have failed to show that administering low-molecular-weight heparin further reduced the overall incidence of DVT. The low-molecular-weight heparin regimens have DVT rates of 12% to 16% in surgical patients and 30% in severely injured patients. This failure to prevent DVT is most likely the result of an inadequate heparin effect due to antithrombin III depletion. Until monitoring of low-molecular-weight heparin becomes more feasible, this failure will persist.

In summary, for patients undergoing a major operation or who are severely injured, we recommend the following measures. Patients without specific contraindications to heparin should be given enough heparin to maintain their aPTT 5 seconds above normal (adjusted dose). Those patients who have a contraindication to heparin and are at a low to moderate risk for thromboembolism should have a mechanical method of prophylaxis used. Those patients with contraindications to heparin who are at high risk should have a caval filter placed.

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REFERENCES

Geerts WH, Code KI, Jay RM, Chen E, Szalai JP: A prospective study of venous thromboembolism after major trauma. N Engl J Med 1994; 331:1601-1606

Geerts WH, Jay R, Code K, et al: Thromboprophylaxis after major trauma—A double-blind randomized controlled trial comparing low-dose heparin and the low-molecular-weight heparin enoxaparin (Abstr). Thromb Haemost 1995; 73:973

Knudson MM, Lewis FR, Clinton A, Atkinson K, Megerman J: Prevention of venous thromboembolism in trauma patients. J Trauma 1994; 37:480-487

Leyvraz PF, Richard J, Bachmann F, et al: Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 1983; 309:954-958

Owings JT, Bagley M, Gosselin R, Romac D, Disbrow E: Effects of critical injury on plasma antithrombin activity: Low antithrombin levels are associated with thromboemholic complications. J Trauma, in press

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Alerts, Notices, and Case Reports

Cerebellar Hemangioblastoma Presenting as Secondary Erythrocytosis and Aspiration Pneumonia

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HEMANGIOBLASTOMAS are rare benign tumors that occupy the central nervous system and other organs such as kidney, liver, and pancreas. They constitute between 1% and 2% of all intracranial tumors, and among posterior fossa tumors, their incidence averages 11%. Hemangioblastomas occur more commonly in men than in women, with the highest incidence being in the third and the sixth decades of life.[1] The association of erythrocytosis with hemangioblastomas, which was first recognized in 1943,[2] occurs in 5% to 30% of cases.[1,3-5]

A cerebellar hemangioblastoma can present either as an isolated finding or as a manifestation of von Hippel-Lindau disease, which consists of retinal hemangioma, renal cell carcinoma or renal cyst, pheochromocytoma, and cerebellar hemangioblastoma. A family history of von Hippel-Lindau disease with one of these manifestations is sufficient to make a diagnosis of von Hippel-Lindau disease.[6] It is an autosomal dominant disease related to a deletion of the tumor suppressor gene on the short arm of chromosome 3. The gene was first discovered by positional cloning in 1989.[7]

Most patients with cerebellar hemangioblastomas present with symptoms due to intracranial hypertension (85%), dizziness and disturbance of equilibrium (37.5%), disturbance of gait (25%), and mental confusion (10%).[1]

Report of a Case

The patient, a 70-year-old woman, was admitted with aspiration pneumonia and hypoxemia. A year before admission, she started having pressure-type occipital headaches as often as three times a week associated with dyspnea on minimal exertion. Five months later, she saw her family physician for these headaches and was found to have a mildly elevated blood pressure of 140/106 mm of mercury and a hematocrit of 0.64 (64%) with a normal leukocyte count, platelet count, and red cell indices. The results of a cardiac workup, including an electrocardiogram and an exercise tolerance test, were normal. A pulmonary workup revealed a normal chest x-ray film, spirometric findings, and arterial blood gas values, with a Pa_{O_2} of 71 mm of mercury with the patient breathing room air and an oxygen saturation of 92%. Over the next six months, she was treated with eight successive phlebotomies. Her symptoms progressed to include ataxia, a 4.5-kg (10-lb) weight loss, and occasional diplopia. Two months later, dysphagia to solids and liquids developed, and she had severe coughing after oral intake. An upper gastrointestinal series showed mild esophageal dysmotility without evidence of reflux, mass, or stricture. A subsequent chest x-ray film was consistent with aspiration pneumonia, with barium observed in the lungs.

On admission, the patient had dyspnea with a respiratory rate of 32 per minute. She was afebrile and had a blood pressure of 150/90 mm of mercury. Examination of her lungs revealed diffuse rhonchi. There was no splenomegaly. The neurologic examination showed nystagmus to lateral gaze. Finger-to-nose and heel-to-shin tests were normal. Her gait was ataxic and broad-based with a tendency to deviate to the right.

Admission laboratory values showed a leukocyte count of 10.9×10^9 per liter (10,900 per mm^3) and a hematocrit of 0.48 (48%), with a simultaneously normal serum erythropoietin level of 19 U per liter (normal, 3.5 to 22.0 U per liter for persons with normal hematocrit, as measured by enzyme-linked immunosorbent assay).[8] Her platelet count was 372×10^9 per liter (372,000 per mm^3). Serum electrolyte values were normal. The Pa_{O_2} was 52 mm of mercury with the patient breathing room air.

Because of the presentation, a cerebellar hemangioblastoma encroaching on the brain stem was suspected. Magnetic resonance imaging of the head with gadolinium enhancement showed an inferior midline cerebellar mass that extended partially through the foramen magnum. The mass had high vascularity and cystic foci, suggesting a hemangioblastoma. There was evidence of mild enlargement of the ventricles, representing partial obstruction of the fourth ventricle (Figure 1).

A cerebral angiogram showed that the mass was supplied by both the right and left anteroinferior cerebellar arteries, both the right and left posteroinferior cerebellar arteries, and the distal aspect of the left superior cerebellar artery (Figure 2). Because of the "on passage" supply, embolization was not feasible.

An intravenous pyelogram showed normal kidneys. A computed tomographic scan of the abdomen showed mild bilateral adrenal hyperplasia with a possible left renal cyst. An ophthalmologic consultation ruled out retinal hemangioblastomas. There was no family history of von Hippel-Lindau disease; therefore, this was considered an isolated case of cerebellar hemangioblastoma without evidence of von Hippel-Lindau disease.

The patient underwent excision of the tumor, and subsequently she had intracerebellar hemorrhage in the

(Farrukh HM: Cerebellar hemangioblastoma presenting as secondary erythrocytosis and aspiration pneumonia. West J Med 1996; 164:169-171)

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Figure 1.—Magnetic resonance imaging of the head with gadolinium enhancement shows the cystic nature of the cerebellar tumor.

resection bed with mass effect. Despite attempted evacuation of the hematoma, the patient went into a deep coma and died within 48 hours. Pathologic examination of the tumor revealed thin-walled capillary vessels mixed with stromal cells, consistent with hemangioblastoma.

Discussion

This patient presented with occipital headaches and erythrocytosis. The absence of associated leukocytosis, thrombocytosis, or splenomegaly ruled against the diagnosis of polycythemia vera and in favor of secondary erythrocytosis. Secondary erythrocytosis is caused by several disorders, including chronic lung disease or alveolar hypoventilation, cardiovascular right-to-left shunt, cobalt toxicity, renal diseases, congenitally decreased 2,3-diphosphoglycerate levels, carboxyhemoglobinemia, adrenocortical hypersecretion, and various tumors.[9-11]

The most common type of tumor associated with secondary erythrocytosis is renal cell carcinoma.[10] Less common are cerebellar and adrenal hemangioblastoma,[10] hepatoma, uterine leiomyoma, ovarian carcinoma, and pheochromocytoma. Usually the red cell indices return to normal after the tumor is resected.[12-14]

The association between cerebellar hemangioblastomas and erythrocytosis was first recognized in 1943.[2] In 1960 it was shown that the fluid aspirated from a cystic cerebellar tumor and administered subcutaneously to fasted rats caused pronounced stimulation of erythropoiesis as measured by the incorporation of ferrous sulfate Fe 59 into the red cells. This was not observed, however, when concentrated urine, plasma, ventricular, or spinal fluid was used.[15] In that study, the investigators were not able to demonstrate the production of red cells by the cerebellar tumor or other extramedullary cells. In 1952 it was suggested that hemangioblastomas may either be erythropoietic or cause erythrocytosis by disturbing oxygenation due to arteriovenous shunts in the hemangioblastoma.[16] Other investigators were later able to show histologically the presence of foci of extramedullary hematopoiesis by the tumor itself. In 1991 islands of normoblasts were observed in 4 of 26 hemangioblastomas studied.[17]

The first radioimmunoassay evidence of the ectopic production of erythropoietin was demonstrated in 1991 in the cyst fluid of a patient with recurrent intracranial hemangioblastomas and von Hippel-Lindau disease.[18]

The most convincing and direct evidence of ectopic erythropoietin production by the tumor was shown when erythropoietin messenger RNA was detected in the tumor of an erythropoietic patient with a cerebellar hemangioblastoma.[13] With the use of Northern blot analysis of cyst fluid from patients with erythrocytosis, a positive hybridization signal with a human erythropoietin complementary DNA probe was noted; in contrast, RNA from tumors of patients without erythrocytosis failed to show a positive signal.

In our patient, the serum erythropoietin level was normal. The same has been observed by other investigators,[12,13] who were unable to detect elevated serum erythropoietin levels in patients with erythrocytosis. This is contrary to the observations in one report in which a patient had an elevated serum erythropoietin level.[18] It is possible that the small amount of erythropoietin produced by hemangioblastomas is potent enough to cause erythrocytosis without causing a substantially elevated serum erythropoi-

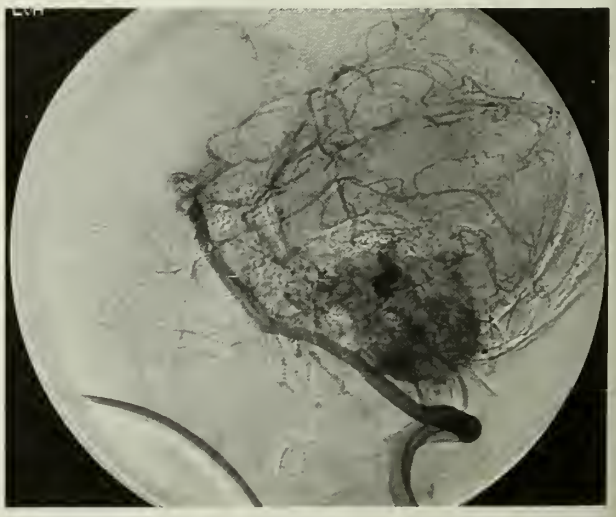

Figure 2.—Cerebral angiography shows the vascularity of the cerebellar tumor.

etin level. Other explanations include intermittent production or the release of erythropoietin[13] or a circadian variation of the erythropoietin level.[19]

Cerebellar hemangioblastomas are benign tumors that can be solid, cystic, or a combination of both. Although they are benign, their course might be malignant because of their tendency to recur as long as ten years after initial tumor excision. The frequency of recurrence is approximately 25%.[1,3,20-22] When the clinical profiles and histopathologic features of 26 patients with recurring and nonrecurring hemangioblastomas were retrospectively examined, patients with recurring tumors tended to be younger, with a mean age of 22.3 versus 43.8 years for nonrecurring tumors; they had a shorter duration of symptoms, a smaller volume of tumor, a higher hematocrit, and the tumors were multicentric.[20] In addition, patients with von Hippel-Lindau disease were prone to recurrent tumors. Men had a higher incidence of tumor recurrence than women. Pathologically recurring tumors were small and noncystic, whereas nonrecurring tumors were larger and highly cystic. In addition, incomplete surgical excision correlated with tumor recurrence.[22]

Total excision is curative. Radiation therapy with 40 to 50 Gy (4,000 to 5,500 rad) over four to six weeks is recommended for tumors not amenable to complete excision, like solid hemangioblastomas that commonly occur in the brain stem. Patients receiving 40 to 50 Gy had a sevenfold higher chance of 15-year survival than patients receiving low-dose radiotherapy of 20 to 30 Gy.[23]

In summary, patients who present with secondary erythrocytosis and neurologic findings should be suspected to have central nervous system hemangioblastomas. Patients with von Hippel-Lindau disease and their families should be counseled because it is an autosomal dominant disorder that carries a poor prognosis if it goes unrecognized.

REFERENCES

1. Constans JP, Meder F, Maiuri F, Donzelli R, Spaziante R, de Divitiis E: Posterior fossa hemangioblastomas. Surg Neurol 1986; 25:269-275

2. Carpenter G, Schwartz H, Walker AE: Neurogenic polycythemia. Ann Intern Med 1943; 19:470

3. Jeffreys R: Clinical and surgical aspects of posterior fossa hemangioblastomas: J Neurol Neurosurg Psychiatry 1975; 38:105-111

4. Waldmann TA: Polycythemia and Cancer, Fifth National Cancer Conference Proceedings, Philadelphia 1964. Philadelphia, Pa, JB Lippincott, 1965, pp 437-443

5. Palmer JJ: Hemangioblastomas: A review of 81 cases. Acta Neurochir (Wien) 1972; 27:125-148

6. Lesho EP: Recognition and management of von Hippel-Lindau disease. Am Fam Physician 1994; 50:1269-1272

7. Latif F, Tory K, Gnarra J, et al: Identification of the von Hippel-Lindau disease tumor suppressor gene. Science 1993; 260:1317-1320

8. Caro J, Erslev A: Erythropoietin assays and their use in the study of anemias. Contrib Nephrol 1988; 66:54-62

9. Golde DW, Hocking WG, Koeffler HP, Adamson JW: Polycythemia: Mechanisms and management. Ann Intern Med 1981; 95:71-87

10. Hammond D, Winnick S: Paraneoplastic erythrocytosis and ectopic erythropoietins. Ann NY Acad Sci 1974; 230:219-227

11. Thorling EB: Paraneoplastic erythrocytosis and inappropriate erythropoietin production: A review. Scand J Haematol Suppl 1972; 17:1-166

12. Burns C, Levine PH, Reichman H, Stock JL: Adrenal hemangioblastoma in von Hippel-Lindau disease as a cause of secondary erythrocytosis. Am J Med Sci 1987; 293:119-121

13. Trimble M, Caro J, Talalla A, Brain M: Secondary erythrocytosis due to a cerebellar hemangioblastoma: Demonstration of erythropoietin mRNA in the tumor. Blood 1991; 78:599-601

14. Ward AA Jr, Folitz EL, Knopp LM: Polycythemia associated with cerebellar hemangiohlastoma. J Neurosurg 1956; 13:248

15. Waldmann TA, Levin EH, Baldwin M: The association of polycythemia with cerebellar hemangiohlastoma. Am J Med 1961; 31:318-323

16. Cramer F, Kimsey W: The cerebellar hemangiohlastomas—Review of 53 cases, with special reference to cerebellar cysts and the association of polycythemia. Arch Neurol Psychiatry 1952; 67:237-252

17. Zec N, Cera P, Towfighi J: Extramedullary hematopoiesis in cerebellar hemangioblastoma. Neurosurgery 1991; 29:34-37

18. Horton JC, Harsh GR IV, Fisher JW, Hoyt WF: Von Hippel-Lindau disease and erythrocytosis: Radioimmunoassay of erythropoietin in cyst fluid from a brainstem hemangioblastoma. Neurology 1991; 41:753-754

19. Wide L, Bengtsson C, Birgegård G: Circadian rhythm of erythropoietin in human serum. Br J Haematol 1989; 72:85-90

20. de la Monte SM, Horowitz SA: Hemangioblastomas: Clinical and histopathological factors correlated with recurrence. Neurosurgery 1989; 25:695-698

21. Silver ML, Henniger G: Cerebellar hemangioma—A clinicopathological review of 40 cases. J Neurosurg 1952; 9:484-494

22. Pennybacker J: Recurrence in cerebellar hemangioblastomas. Z Neurochir 1954; 14:63-75

23. Sung DI, Chang CH, Harisiadis L: Cerebellar hemangioblastomas. Cancer 1982; 49:553-555

Pulmonary Hemorrhage in an Adolescent With Henoch-Schönlein Purpura

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HENOCH-SCHÖNLEIN purpura is a vasculitic syndrome, primarily observed in children, that is characterized by a nonthrombocytopenic purpuric rash, arthralgia or arthritis, abdominal pain often with gastrointestinal bleeding, and nephritis. A high frequency of decreased diffusion capacity in children has been demonstrated with Henoch-Schönlein purpura,[1] but clinically important pulmonary disease is unusual. We report the case of a 15-year-old boy with Henoch-Schönlein purpura in whom acute, bilateral, life-threatening pulmonary hemorrhage developed.

Report of a Case

The patient, a previously healthy 15-year-old boy, was admitted to a local hospital because for two days he had had fever, sore throat, arthralgia, abdominal pain, and an urticarial or purpuric rash on his extremities and buttocks. He was diagnosed with streptococcal pharyngitis by throat culture and was treated with penicillin. His blood pressure progressively increased, and he had heme-positive stools, hematuria, and proteinuria. The rash pro-

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Figure 1.—A chest radiograph was taken about 3 hours after the patient's acute respiratory decompensation. A large right pleural effusion has resolved with the placement of a chest tube. There are new, diffuse alveolar infiltrates with air bronchograms throughout the left lung fields.

gressed to large, palpable purpuric lesions on the distal upper extremities, thighs, and buttocks, and he was diagnosed with Henoch-Schönlein purpura.

Ten days after his symptoms began, the patient was transferred to Madigan Army Medical Center (Tacoma, Washington) where the diagnosis was confirmed by the presence of a palpable purpuric rash primarily on the lower extremities and buttocks, severe arthralgia and arthritis, abdominal pain associated with grossly bloody stools, and nephritis. His blood pressure was 172/104 mm of mercury despite treatment with nifedipine, hydralazine hydrochloride, and furosemide. Laboratory tests elicited the following values: leukocyte count, 36.5×10^9 per liter (36,500 per mm^3), with a predominance of neutrophils; hematocrit, 0.39 (39%); platelet count, 313×10^9 per liter (313,000 per mm^3); erythrocyte sedimentation rate, 7 mm per hour; serum urea nitrogen, 25.5 mmol per liter (71 mg per dl); serum creatinine, 115 μmol per liter (1.3 mg per dl); serum albumin, 18 grams per liter; C3, 0.6 grams per liter (normal, 0.6 to 1.2), and C4, 0.15 grams per liter (normal, 0.2 to 0.5); and a negative antinuclear antibody (ANA) titer.

Two days after admission, a right pleural effusion developed, and a thoracentesis was done, removing 300 ml of pleural fluid—a transudate, with a ratio of pleural fluid lactate dehydrogenase (LDH) to serum LDH of 0.07. About an hour later, the patient became acutely dyspneic, and his oxygen saturation decreased abruptly to 80% while he was receiving 100% oxygen. An endotracheal tube was inserted, and large amounts of red frothy secretions were suctioned from the trachea. Mechanical ventilation was begun and a right chest tube placed; the pleural fluid evacuated by the chest tube was not grossly bloody (pleural fluid erythrocyte count, 2.44×10^9 per liter [2,440 per mm^3]). A chest radiograph revealed new infiltrates in the left upper and lower lung fields, no pneumothorax, and resolution of the right pleural effusion (Figure 1). His hematocrit decreased from 0.32 to 0.22, and he was transfused with four units of packed red blood cells. A ventilation-perfusion lung scan was interpreted as showing a low probability for pulmonary embolus. A pulmonary artery catheter was placed, and his initial pulmonary capillary wedge pressure was 28 mm of mercury, which decreased to 18 mm of mercury within several hours. He had an elevated cardiac index (>7.5) and low systemic vascular pressures, and an echocardiogram documented normal ventricular function.

ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
LDH = lactate dehydrogenase
SLE = systemic lupus erythematosus

A course of intravenously administered methylprednisolone sodium succinate, 125 mg every six hours, was started. He improved, and mechanical ventilation was discontinued after three days. Two days later, he became acutely hypoxemic and again required mechanical ventilation. A chest radiograph at that time revealed clearing of the left lung infiltrates and a new right upper lobe infiltrate. His hematocrit decreased abruptly from 0.27 to 0.23. He improved rapidly and was extubated two days later. Within a week, his lung infiltrates had completely resolved, he had no respiratory symptoms, and he had normal oxygen saturation while breathing room air. His regimen of methylprednisolone lasted a total of nine days: 500 mg per day for four days, 300 mg per day for four days, and 160 mg for one day; this was followed by a course of oral prednisone for four days. He required no further immunosuppressive therapy.

Ten months after the incident, the patient had no respiratory symptoms and had normal pulmonary function: forced vital capacity and forced expired volume in one second, both 100% of predicted values; total lung capacity, 99% of predicted values; and single-breath diffusing capacity, 88% of predicted values. His hematuria, hypertension, and proteinuria had completely resolved, and he had had no recurrence of skin rashes, arthralgia, or abdominal pain. He remains disease-free at the time of this report, more than 18 months since his initial presentation.

Discussion

Henoch-Schönlein purpura, a vasculitic syndrome of unknown cause, is usually a mild, self-limited disease most commonly affecting children between 2 and 10 years of age, but it has been observed in older children and adults.[2-4] Serious complications of the syndrome usually involve the kidneys (nephritis) and occasionally the gastrointestinal tract or the central nervous system. Clinically important pulmonary complications are rare.

Our patient had three of the four American College of Rheumatology criteria for Henoch-Schönlein purpura: palpable purpura without thrombocytopenia, age 20 years or younger at disease onset, and gastrointestinal bleeding.[5]

The fourth criterion, extravascular or perivascular granulocytes on skin biopsy, was not met because our patient did not have a biopsy. The differential diagnosis for this patient includes other vasculitic diseases that have been associated with pulmonary hemorrhage: Wegener granulomatosis, systemic lupus erythematosus (SLE), and polyarteritis nodosa. Our patient had a normal ANA level, indicating a less than 0.14% chance of having SLE.[6(p1039)] His complement levels were slightly decreased, which is consistent with SLE, but about 19% of patients with Henoch-Schönlein purpura also have low levels.[5] Wegener granulomatosis can be difficult to differentiate from Henoch-Schönlein purpura early in the disease course.[7] We did not assess for antineutrophilic cytoplasmic antibodies primarily because at the time of evaluation, the diagnosis of Henoch-Schönlein purpura was not in question. Nevertheless, we think that our patient did not have Wegener granulomatosis because he did not present with any upper respiratory tract clinical findings, and without any long-term immunosuppressive therapy, he has remained free of respiratory symptoms for more than a year after the onset of the illness. This would be extremely unusual for a patient with Wegener granulomatosis.[8]

Polyarteritis nodosa can present similarly to Henoch-Schönlein purpura. There are no specific laboratory tests that can confirm a diagnosis of polyarteritis nodosa, but histologic examination of involved tissues can be useful. We did not do any biopsies on our patient, but we think that, although we did not rule out polyarteritis nodosa, it was unlikely in our patient for the following reasons. It is rare in children. The rash of this disorder tends to persist for weeks and to extend over the entire body,[9] whereas our patient had the characteristic Henoch-Schönlein purpuric rash over the lower extremities and buttock, which resolved within two weeks. Polyarteritis nodosa is characterized by a progressive course with an extremely high mortality if not treated with long-term immunosuppressive therapy.[6(pp1238-1239),9,10] Our patient, after receiving just one short course of corticosteroids, has remained free of any skin, renal, or lung problems for more than a year since his acute illness began. Although possible, this would be highly unlikely if he had polyarteritis nodosa.[6]

Even though serious pulmonary complications of Henoch-Schönlein purpura are rare, they have been reported, with the most common one being pulmonary hemorrhage. We identified 15 cases of pulmonary hemorrhage associated with this disorder reported in the literature.[2-4,12-18] Of the 15 patients, 6 died as a result of the pulmonary hemorrhage, and all suffered serious morbidity. Of the 15 patients, 11 were either adolescents or adults, and all had severe, multiorgan involvement.

Although the vast majority of patients in whom Henoch-Schönlein purpura develops are 2 to 10 years old, most of those reported to have associated pulmonary hemorrhage have been adolescents and adults. This suggests that pulmonary hemorrhage is more common in adolescents and adults with this syndrome than it is in younger children.

The principal cause of pulmonary hemorrhage in Henoch-Schönlein purpura is a vasculitis of the small pulmonary blood vessels, especially the capillaries.[13,14,17] This patient's elevated pulmonary capillary wedge pressure might have increased his risk of pulmonary hemorrhage. In addition, he had mild uremia that could have affected platelet function, further predisposing him to hemorrhage. Corticosteroids have been used in the hope of ameliorating the vasculitis, but their efficacy has not been established. Both lack of response[14] and dramatic improvement[2] have been reported. Nevertheless, it seems prudent to use them in high doses (200 to 1,000 mg of methylprednisolone per day) until the event has resolved and then to taper.

Most of the patients reported in the literature with Henoch-Schönlein purpura and pulmonary hemorrhage were older and had more severe multiorgan involvement than the typical child with this syndrome. Patients with severe manifestations of Henoch-Schönlein purpura, especially adolescents and adults, are at risk of having acute, life-threatening pulmonary hemorrhage. Although not proved, early treatment of this high-risk group with corticosteroids should be considered in the hope of decreasing the morbidity and mortality of this serious complication.

REFERENCES

1. Chaussain M, de Boissieu D, Kalifa G, et al: Impairment of lung diffusion capacity in Schönlein-Henoch purpura. J Pediatr 1992; 121:12-16

2. Olson JC, Kelly KJ, Pan CG, Wortmann DW: Pulmonary disease with hemorrhage in Henoch-Schönlein purpura. Pediatrics 1992; 89:1177-1181

3. Roth DA, Wilz DR, Theil GB: Schönlein-Henoch syndrome in adults. Q J Med 1985; 55:145-152

4. Cream JJ, Gumpel KM, Peachey RDG: Schönlein-Henoch purpura in the adult. Q J Med 1970; 156:461-484

5. Mills JA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. Arthritis Rheum 1990; 33:1114-1121

6. Kelly WN, Harris ED Jr, Ruddy S, Sledge C: Textbook of Rheumatology, 4th edition. Philadelphia, Pa, WB Saunders, 1993

7. Hall SL, Miller LC, Duggan E, Mauer SM, Beatty EC, Hellerstein S: Wegener granulomatosis in pediatric patients. J Pediatr 1985; 106:739-744

8. Rottem M, Fauci A, Hallahan CW, Kerr GS, Leavitt RY, Hoffman GS: Wegener granulomatosis in children and adolescents: Clinical presentation and outcome. J Pediatr 1993; 122:26-31

9. Reimold EW, Weinberg AG, Fink CW, Battles ND: Polyarteritis in children. Am J Dis Child 1976; 130:534-541

10. Magilavy DB, Petty RE, Cassidy JT, Sullivan DB: A syndrome of childhood polyarteritis. J Pediatr 1977; 91:25-30

11. Cohen RD, Conn DT, Ilstrup DM: Clinical features, prognosis and response to treatment in polyarteritis. Mayo Clin Proc 1980; 55:146-155

12. Marandian MH, Ezzati M, Behvad A, Moazzami P, Rakhchan M: Manifestations pulmonaires du purpura rhumatoïde de Schönlein-Henoch, chez un enfant de huit ans. Arch Fr Pediatr 1982; 39:255-257 (Engl Abstr)

13. Kathuria S, Cheifee G: Fatal pulmonary Henoch-Schönlein syndrome. Chest 1982; 82:654-656

14. Weiss VF, Naidu S: Fatal pulmonary hemorrhage in Henoch-Schönlein purpura. Cutis 1979; 23:687-688

15. Payton CD, Allison MEM, Boulton-Jones JM: Henoch Schönlein purpura presenting with pulmonary haemorrhage. Scot Med J 1987; 32:26-27

16. Jacome AF: Pulmonary hemorrhage and death complicating anaphylactoid purpura. South Med J 1967; 60:1003-1004

17. Markus HS, Clark JV: Pulmonary haemorrhage in Henoch-Schönlein purpura. Thorax 1989; 44:525-526

18. Wright WK, Krous HF, Griswald WR, et al: Pulmonary vasculitis with hemorrhage in anaphylactoid purpura. Pediatr Pulmonol 1994; 17:269-271

Late Complications of Infection With *Opisthorchis viverrini*

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OPISTHORCHIS VIVERRINI is a parasite that commonly infects cats, dogs, and many fish-eating mammals; humans who ingest infested fish may become incidental hosts. As much as 90% of the population of northeastern Thailand and Laos harbors this parasite, and cholangiocarcinoma may develop in as many as half of those infected.[1-3] We report a case of cholangiocarcinoma associated with *O viverrini* infection in a Laotian immigrant, and we discuss its public health implications.

Report of a Case

The patient, a 43-year-old woman who emigrated from Laos at age 35, was admitted to a hospital because of progressive fatigue and abdominal pain for two months and jaundice for two weeks. Her abdominal pain was sharp, unremitting, and bandlike across her abdomen. She reported having no bowel movements for five days before admission. She did not have diarrhea, melena, hematochezia, nausea, vomiting, fever, chills, or night sweats. She had a bout of mild upper abdominal pain as a young adult and was told she had "cysts in the liver." There was no known history of parasitic infection, blood transfusions, hepatitis, or tuberculosis. Her medications included ibuprofen as needed for pain and Chinese herbs. There was no family history of cancer or liver disease. Further relevant history included about a 9-kg (20-lb) weight loss attributed to a grief reaction following the death of her husband in a motor vehicle accident eight months before admission.

On physical examination, she was small, ill-appearing, and icteric, and she appeared older than her stated age. Her temperature was 37°C, pulse rate 98 beats per minute, blood pressure 115/65 mm of mercury, and respiratory rate 16 breaths per minute. Relevant findings included a protuberant abdomen, diminished bowel sounds, a positive fluid wave, and diffuse mild tenderness without guarding or rebound. Her liver was nodular and measured approximately 14 cm by percussion. The spleen was not felt. The results of a pelvic and rectal examination were normal.

Routine laboratory test results were remarkable for mild leukocytosis with a leftward shift, anemia, hypokalemia, and azotemia. The aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, and tumor marker CA 125 levels were elevated (Table 1).

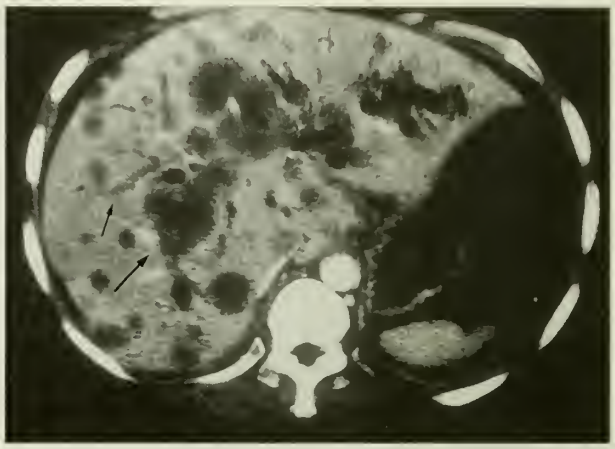

Figure 1.—An abdominal computed tomographic study shows multiple masses throughout the liver (long arrow) and dilated intrahepatic biliary ducts (short arrow).

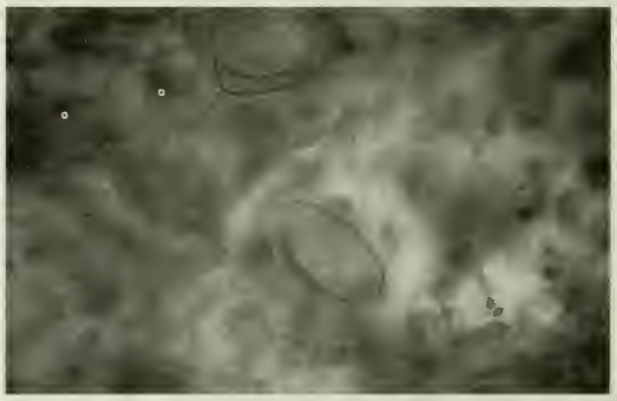

Figure 2.—Ovoid eggs typical of *Opisthorchis viverrini* are found in fine-needle aspirate of the patient's liver (original magnification, × 900).

An abdominal ultrasonogram showed moderate ascites and a markedly heterogeneous texture of the liver that was suggestive of multiple hepatic masses. The gallbladder wall was circumferentially but mildly thickened to 4 mm, but no gallstones were seen. An abdominal paracentesis was done (Table 1), and cytologic examination of the fluid did not elicit malignancy. An abdominal computed tomographic (CT) scan showed multiple masses in the liver, dilated intrahepatic biliary ducts, and a thrombosed portal vein (Figure 1). A CT-guided fine-needle aspirate of a liver lesion showed a poorly differentiated adenocarcinoma, consistent with cholangiocarcinoma, and ovoid parasite eggs typical of *Opisthorchis viverrini* (Figure 2).

We informed the patient and her family of her poor prognosis and together decided on a conservative approach. She was treated for a urinary tract infection and given blood transfusions for anemia. A therapeutic large-volume paracentesis was done before she was discharged.

(Chiu A, Neff M, Garcia G: Late complications of infection with *Opisthorchis viverrini*. West J Med 1996; 164:174-176)

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TABLE 1.—*Admission Laboratory Test Results in a 43-Year-Old Woman With Abdominal Pain and Jaundice*

*Laboratory Test, units**	*Patient Value*		*Normal Value*
Aspartate aminotransferase, U/liter	302		5-35
Alanine aminotransferase, U/liter	166		7-56
Alkaline phosphatase, U/liter	655		43-122
Lactate dehydrogenase, U/liter	4,802		297-537
Total bilirubin, μmol/liter ((mg/dl)	113	(6.6)	3-18 (0.2-1.0)
Albumin, grams/liter (grams/dl)	31	(3.1)	33-50 (3.3-5.0)
CA 125 (U/ml)		(702)	(0-16)
Ascitic fluid			
Leukocyte count, × 10^9/liter (/mm^3)	1.7	(1,700)	
Differential cell count, fraction of 1 (%)			
Neutrophils	0.04	(4)	
Lymphocytes	0.53	(53)	
Monocytes	0.39	(39)	
Erythrocyte count, × 10^9/liter (/mm^3)	1.5	(1,500)	
Lactate dehydrogenase, U/liter	1,650		
Total protein, grams/liter (grams/dl)	3.1	(31)	
Glucose, mmol/liter (mg/dl)	5.6	(101)	
Albumin, grams/liter (grams/dl)	14	(1.4)	

*Laboratory values are given in Système International (SI) units, with conventional units given in parentheses.

She was sent home with a patient-controlled anesthesia pump for administering subcutaneous morphine. As an outpatient, she received another blood transfusion and large-volume paracentesis was again done, but she died two weeks after hospital discharge. Permission for an autopsy was not given.

The public health department screened her family for stool ova and parasites. Three of her six children (ages 13, 18, and 24) and her brother had stool specimens said to be positive for *Clonorchis* species ova (30 by 15 mm), which are slightly larger but otherwise essentially indistinguishable from *O viverrini* ova (30 by 12 mm).[4]

Discussion

Opisthorchis viverrini is an organism belonging to the class Trematoda (fluke). It is small (7 to 12 mm by 1.5 to 3 mm), yellow-red, leaflike in shape, rounded posteriorly, and tapered at its anterior end, with both an oral and a smaller ventral sucker. In endemic areas, people or other mammals become infected by eating raw or undercooked fish that carry the metacercariae. The ingested metacercariae excyst in the duodenum and migrate up the ampulla of Vater to the bile ducts, where they mature in about a month. The adult worms produce eggs that are then passed into the bile ducts and into the feces. The eggs hatch after being ingested by a *Bithynia* species snail, the first intermediate host. Cercariae emerge from the snail and are free-swimming organisms before invading freshwater fish and crayfish, the second intermediate hosts, where they encyst as metacercariae.[3,4] The complete life cycle is about four months. Adult worms have a life span of more than ten years.

Opisthorchis viverrini is the most common foodborne parasite identified in Thailand, where an estimated 6 to 7 million people are infected with it. This costs the country about $65 million per year in wage loss and $19.4 million per year in medical care.[5] People from endemic regions (Thailand, Laos, Cambodia, and Malaysia) eat ground, raw, and salt-fermented freshwater fish daily.[3,6] They usually become infected in their childhood or adolescent years and carry this infection throughout their lifetime if they are not treated. Each time an infected raw fish is ingested, the worm burden increases.[3]

Most persons infected with *O viverrini* are asymptomatic. As the worm burden increases, usually in those older than 30 years, anorexia, weakness, nausea, diarrhea, flatulence, and episodes of right upper quadrant and epigastric pain may develop. On physical examination, acutely infected patients may have fever, jaundice, and tender hepatomegaly. Signs and symptoms due to complications of opisthorchiasis include cholecystitis, cholangitis, obstructive jaundice, cholelithiasis, and cholangiocarcinoma.[1,3,4]

Although the results of laboratory tests of hepatic function are often within normal limits, acute infections may be associated with elevated serum bilirubin levels and other indices of abnormal liver function. Eosinophilia may be seen and, when present, is usually below 20%.[3,4] Asymptomatic hepatobiliary abnormalities may be observed by ultrasonography: enlargement of the liver and gallbladder, decreased gallbladder contractility, the presence of sludge, and enhanced echogenicity of portal vein radicles.[3] Pathologic changes in the bile ducts are related to the intensity and duration of infection. They include inflammatory cell exudation and desquamation of the epithelial lining, with the subsequent development of adenomatous hyperplasia and periductal fibrosis.[3,4]

The diagnosis is usually made by identifying the eggs in stool specimens, although eggs will also be present in duodenal aspirates and bile from any source. Egg produc-

tion can be intermittent; thus, stool specimens from different days may have to be examined to make the diagnosis. If there is obstructive jaundice—as in our patient—eggs may not pass into the intestine, and stool specimens may be persistently normal.[2,4]

In our patient, the diagnosis was established after a liver biopsy was done. We thought that her history, radiographic studies, and histologic findings collectively strengthened the diagnosis of adenocarcinoma from bile duct origin due to *O viverrini* infection. Furthermore, her CA 125 tumor marker level was high, and reports suggest that CA 125 may be a specific tumor marker for cholangiocarcinoma.[7,8] We assume that the parasite eggs found in the stool specimens of the patient's family members are indeed a species of *Opisthorchis* and not that of *Clonorchis*. The two parasite eggs are difficult to distinguish, and the patient's family came from the same area in Laos where *Opisthorchis* species infestations are much more common than are infestations with *Clonorchis* species.

The carcinogenic event in cholangiocarcinoma associated with *O viverrini* is not known. Rapid cell turnover due to chronic cholangitis may enhance the unregulated growth of altered cells. An important interaction between the ingestion of nitrosamines (found in fermented fish) and *O viverrini* infection probably exists in the development of cholangiocarcinoma.[3,9] The chewing of betel nut in the same population seems to be an independent risk factor for cholangiocarcinoma.[6]

The treatment of *O viverrini* infection is simple and consists of the administration of praziquantel, 25 mg per kg by mouth three times on a single day. Side effects from treatment are common and may include nausea, vomiting, abdominal pain, dizziness, myalgias, headache, and fatigue. They are generally well tolerated and usually abate within 48 hours.[2] The eggs generally disappear from the stools in a week, but symptoms and signs may take months to resolve. Alternative therapies include the administration of mebendazole, 30 mg per kg daily for 20 to 30 days, with cure rates of 89% to 94%; and albendazole, 400 mg twice a day for seven days, with cure rates of 63%.

It is evident that *O viverrini* infection can be fatal if untreated. Because people from Thailand and Laos have become common immigrants to our country, it is important for physicians in the United States to be cognizant of this possibly fatal disease. In 1994 the Santa Clara County (California) Refugee Program screened 2,101 Southeast Asian refugees for stool ova and parasites; 932 of these were positive. Many counties, however, do not screen refugees because of lack of funds. The positive stool specimens in our patient's family members underscore the importance of screening relatives from the same area and further justify the screening of immigrants as they enter the United States because this disease is easily treated before fatal cholangiocarcinoma develops.

REFERENCES

1. Upatham ES, Viyanant V, Kurathong S, et al: Relationship between prevalence and intensity of *Opisthorchis viverrini* infection, and clinical symptoms and signs in a rural community in northeast Thailand. Bull WHO 1984; 62:451-461

2. Muller RL: Liver fluke infection, *In* Jordan MC (Ed): Infectious Diseases—A Modern Treatise of Infectious Processes, 4th edition. Philadelphia, Pa, JB Lippincott, 1989, pp 841-844

3. Haswell-Elkins MR, Satarug S, Elkins DB: *Opisthorchis viverrini* infection in northeast Thailand and its relationship to cholangiocarcinoma. J Gastroenterol Hepatol 1992; 7:538-548

4. Dooley JR, Neafie RC: Clonorchiasis and opisthorchiasis, *In* Binford CH, Connor DH (Eds): Pathology of Tropical and Extraordinary Diseases—An Atlas, 2nd edition. Washington, DC, Armed Forces Institute of Pathology, 1976, pp 509-516

5. Loaharanu P, Sornmani S: Preliminary estimates of economic impact of liver fluke infection in Thailand and the feasibility of irradiation as a control measure. Southeast Asian J Trop Med Public Health 1991; 22 (suppl):384-390

6. Parkin DM, Srivatanakul P, Khlat M, et al: Liver cancer in Thailand—I. A case-control study of cholangiocarcinoma. Int J Cancer 1991; 48:323-328

7. Ker CG, Chen JS, Lee KT, Sheen PC, Wu CC: Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. J Gastroenterol Hepatol 1991; 6:505-508

8. Pungpak S, Akai PS, Longenecker M, Ho M, Befus AD, Bunnag D: Tumour markers in the detection of opisthorchiasis-associated cholangiocarcinoma. Trans R Soc Trop Med Hyg 1991; 85:277-279

9. Srivatanakul P, Ohshima H, Khlat M, et al: *Opisthorchis viverrini* infestation and endogenous nitrosamines as risk factors for cholangiocarcinoma in Thailand. Int J Cancer 1991; 48:821-825

Topics in Primary Care Medicine

Diagnostic Enigmas in Thyroid Disease

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Several advances have greatly facilitated the diagnosis of thyroid disease. They include the development of specific and highly sensitive methods for measuring thyroid-stimulating hormone (TSH, thyrotropin) levels and the low concentrations of free or unbound thyroid hormone in serum and to evaluate the use of fine-needle aspiration cytology as the primary diagnostic tool in nodular disease. The American Thyroid Association has issued guidelines for the use of laboratory tests in thyroid disease, and these were updated in 1993.[1] Nonetheless, accurate diagnosis still rests on the correct interpretation of test results in specific clinical or pathophysiologic contexts. I present five cases to illustrate this principle. I have used the second-person format in presenting these cases so as to involve readers in the problem-solving exercise.

Report of Cases

Patient 1

You are asked to see a 51-year-old man in consultation. His principal symptoms are nervousness, fatigue, and weight loss of about a month's duration. He has been taking amiodarone, 200 mg twice a day, for the past four months for recurrent tachycardia. His medical history is relevant for a small goiter since childhood. A physical examination discloses sinus tachycardia, warm moist skin, lid lag, a small multinodular goiter, and a fine tremor.

You confirm the diagnosis of thyrotoxicosis with a serum free thyroxine (T_4) level of 30 pmol per liter (normal, 9 to 24) and an undetectable serum TSH level (normal, 0.5 to 5.5 mU per liter). To elucidate the basis of the thyrotoxicosis, you obtain a thyroid radioactive iodine uptake (RAIU) measurement; the 24-hour value is 0.02 (2%; normal, 0.12 to 0.30).

The RAIU value not only serves as a direct index of thyroid function, but also varies inversely with the size of the body iodine pool. In patient 1, a low RAIU level is due to expansion of the body iodine pool as a result of the iodine excess derived from amiodarone. Amiodarone contains 37% iodine by weight, and a single 200-mg tablet releases about 6 mg of free iodine. Moreover, because it is stored in adipose tissue, amiodarone is cleared slowly, and the release of iodine may continue for several months after the drug is withdrawn. The iodine excess can lead to increased hormone synthesis and secretion in a gland with autonomous foci, as in a nodular goiter, or can aggravate preexisting hyperthyroidism (Jod-Basedow's disease).[2] In addition, amiodarone can produce a cytotoxic effect in the thyroid, with follicle disruption and the release of T_4 and triiodothyronine (T_3) into the circulation, reminiscent of what occurs in thyroiditis.[3] Either mechanism may be responsible for the thyrotoxicosis in patient 1. Thyrotoxicosis may be induced at any time during the course of amiodarone treatment, and it often emerges rapidly. (In patients with defective organic binding of iodine—those with Hashimoto's thyroiditis, for instance—iodine released from amiodarone may lead to hypothyroidism rather than thyrotoxicosis.[2])

The patient's regimen of amiodarone is discontinued, and the thyrotoxicosis resolves over the next two months.

The management of iodine-induced thyrotoxicosis entails withdrawing the source and, in severe cases, the use of potassium perchlorate to inhibit iodide transport in conjunction with methimazole to inhibit hormone synthesis. When amiodarone cannot be withdrawn because of dangerous arrhythmias that are resistant to the use of other drugs, thyroidectomy has been undertaken with excellent results.

Patient 2

You are called to an intensive care unit to evaluate the presence of confusing thyroid test values in a 76-year-old woman. The serum free T_4 level is 6 pmol per liter and the total T_3 value 0.2 nmol per liter (15 ng per dl; normal, 1.4 to 2.6 nmol per liter), but the serum TSH level is normal at 5.0 mU per liter. The patient had been admitted a week earlier with septic shock due to a urinary tract infection and has been receiving dopamine hydrochloride and hydrocortisone sodium succinate for hemodynamic support, as well as antibiotics. A physical examination reveals a hoarse voice and dry skin, and "hung-up" deep tendon reflexes are elicited.

You conclude that the patient has hypothyroidism and begin a regimen of levothyroxine sodium, 100 μg, and liothyronine sodium, 25 μg, intravenously daily. The patient improves remarkably over the next several days, and the dopamine and hydrocortisone are slowly withdrawn. A week later, the free T_4 level is 14 pmol per liter, and the TSH concentration is 24 mU per liter.

This case illustrates the effects of both severe nonthyroid illness and certain pharmacologic agents on thyroid

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ABBREVIATIONS USED IN TEXT

RAIU = radioactive iodine uptake
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

test results in a patient with primary hypothyroidism. The normal serum TSH level might indicate that the greatly depressed serum T_3 and free T_4 values were due to severe nonthyroid illness rather than to hypothyroidism. The patient was receiving dopamine and glucocorticoid, however, both of which will suppress TSH secretion, even in a patient with primary hypothyroidism.[4] Moreover, in contrast to the decreased serum total T_3 and T_4 values, the serum free T_4 concentration is almost always normal in patients with nonthyroid illness, which was not the case in patient 2.[5,6] This last feature is important because euthyroid patients can show transient elevations in serum TSH levels during recovery from severe nonthyroid illness. This case also shows the salutary effect of the judicious replacement of thyroid hormone on cardiovascular function in patients with hypothyroidism.[7]

Patient 3

The patient, a 50-year-old man, is referred to you because of apparent resistance to thyroid hormone. The patient was diagnosed with primary nongoitrous hypothyroidism two months previously, and treatment with levothyroxine sodium, 100 μg every day, was started. A week later, the serum TSH level was still 70 mU per liter, and consequently, the levothyroxine dosage was progressively increased over the next six weeks to 400 μg per day because of persistently elevated serum TSH levels. The TSH level now is 20 mU per liter, and the free T_4 value is 30 pmol per liter.

You reduce the levothyroxine dosage to 150 μg per day and plan to check the serum TSH level in several weeks. Four weeks later, the serum TSH level is 2 mU per liter.

This case illustrates the failure to recognize that a period of four to six weeks is usually required to reflect the effect of an increase in levothyroxine dosage on serum TSH levels. Also important in this case are the possible adverse consequences of excessive dosing of thyroid hormone on the cardiovascular system of a 50-year-old man with hypothyroidism.

Some months later, you are asked to see the patient again because the serum TSH level has increased from 2 to 12 mU per liter despite no change in levothyroxine dosage. The free T_4 value is 15 pmol per liter. Two possibilities could account for this phenomenon. First, the patient may be noncompliant with his levothyroxine regimen and may have only taken it in the week preceding his office visit. Second, the patient may be taking another drug that interferes with the intestinal absorption of levothyroxine. Such drugs include bile acid sequestrants, ferrous sulfate, aluminum hydroxide, and sucralfate.[8,9] Indeed, in the interim, patient 3 had been given sucralfate for peptic ulcer disease. By separating the ingestion of levothyroxine and these drugs to different times of the day, this effect can be avoided.

You instruct the patient to take the levothyroxine about eight hours before taking the sucralfate. Six weeks later, the serum TSH value is 2.3 mU per liter.

Patient 4

The patient, a 33-year-old woman, is referred to you by her obstetrician. She delivered a normal, full-term infant three months before the referral who is currently being breast-fed. For the past several weeks, the patient has noted fatigue, palpitations, and a sense of being "wired." Thyroid test values obtained by the obstetrician include a serum TSH level of 0.16 mU per liter and a free T_4 value of 24 pmol per liter. She has no past history of thyroid disorder, but her mother has Hashimoto's thyroiditis. A physical examination reveals sinus tachycardia and a small, nontender goiter, but no eye signs or other abnormal findings.

You conclude that the patient has mild thyrotoxicosis due either to postpartum thyroiditis or to Graves' disease. A thyroid RAIU measurement would afford the necessary discrimination because the value is low in patients with postpartum thyroiditis and high in those with Graves' disease. Because she is unwilling to interrupt breast-feeding, however, a thyroid RAIU cannot be done. Accordingly, you obtain measurements of serum TSH-receptor and thyroperoxidase antibodies. The TSH-receptor antibody is absent, but thyroperoxidase antibody is present in high titer, strongly suggesting that the patient has postpartum thyroiditis rather than Graves' hyperthyroidism. You elect to monitor her without treatment. A month later, her symptoms have resolved, and the serum TSH level is now 2 mU per liter. (Were this patient not pregnant, she would be given the diagnosis of Hashimoto's thyroiditis, which can occasionally present with transient hyperthyroidism, although in this case the thyroid RAIU is usually increased.)

This case exemplifies the disorder of postpartum thyroiditis, which occurs in about 5% of postpartum women.[10] The clinical manifestations of thyrotoxicosis are mild, often overlooked, and resolve spontaneously. The thyrotoxic phase may be followed by mild hypothyroidism that also resolves spontaneously after several months. This disorder may recur in subsequent pregnancies. Women with the thyroperoxidase antibody are at increased risk for postpartum thyroiditis, and the emergence of the disorder in the postpartum period is due to a loss of the immune tolerance that characterizes the pregnant state. In about a third of the patients, permanent hypothyroidism develops several years later.

Patient 5

You are asked to see a 69-year-old woman on the orthopedic service who was found to have a thyroid nodule. She had been admitted several days earlier because of acute pain resulting from a fracture through a lytic lesion in the right femur. Her history is negative for thyroid disease. Studies to date include a normal mammogram,

chest roentgenogram, serum protein electrophoresis, and urinalysis. On examination, there is a firm, nontender, 5.5 × 3.5 cm nodule in the left lobe of the thyroid without regional lymphadenopathy. The rest of the examination is unremarkable.

You do a fine-needle aspiration of the thyroid nodule. Cytologic examination reveals highly atypical cells with vacuolated cytoplasm, consistent with adenocarcinoma.

The patient undergoes a hemiarthroplasty of the right femur. Histopathologic examination of the excised tissue reveals clear cells similar to what had been found in the thyroid aspirate. A computed tomographic scan of the abdomen is done and reveals a 12-cm mass arising from the upper pole of the left kidney, consistent with renal adenocarcinoma.

In necropsy series, about 10% of patients dying with a malignant neoplasm are found to have metastatic involvement of the thyroid, malignant melanoma, and carcinoma of the breast accounting for more than half of the cases, with the rest being due to renal, lung, head and neck, and hematologic and lymphoid neoplasms. On the other hand, metastatic disease manifesting as a palpable thyroid nodule is uncommon and is seen principally with renal adenocarcinoma.[11] A palpable thyroid nodule usually emerges months or years after the primary renal lesion has been identified.[12] It may occasionally be the presenting manifestation of an occult primary lesion. Radionuclide scintigraphy or ultrasonography of the thyroid will not afford differentiation from a primary thyroid neoplasm, whereas fine-needle aspiration cytology will provide the necessary discrimination. The case under discussion points up the importance of fine-needle aspiration as the initial procedure in the evaluation of a thyroid nodule.

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E. Alejandro Sweet-Cordero, MD, while a medical student, participated in the workup of patient 5.

REFERENCES

1. Becker DV, Bigos ST, Gaitan E, et al: Optimal use of blood tests for assessment of thyroid function (Letter). JAMA 1993; 269:2736-2737

2. Woeber KA: Iodine and thyroid disease. Med Clin North Am 1991; 75:169-178

3. Roti E, Minelli R, Gardini E, Bianconi L, Braverman LE: Thyrotoxicosis followed by hypothyroidism in patients treated with amiodarone—A possible consequence of a destructive process in the thyroid. Arch Intern Med 1993; 153:886-892

4. Kaptein EM, Spencer CA, Kamiel MB, Nicoloff JT: Prolonged dopamine administration and thyroid hormone economy in normal and critically ill subjects. J Clin Endocrinol Metab 1980; 51:387-393

5. Surks MI, Hupart KH, Pan C, Shapiro LE: Normal free thyroxine in critical nonthyroidal illnesses measured by ultrafiltration of undiluted serum and equilibrium dialysis. J Clin Endocrinol Metab 1988; 67:1031-1039

6. Franklyn JA, Black EG, Betteridge J, Sheppard MC: Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. J Clin Endocrinol Metab 1994; 78:1368-1371

7. MacKerrow SD, Osborn LA, Levy H, Eaton P, Economou P: Myxedema-associated cardiogenic shock treated with intravenous triiodothyronine. Ann Intern Med 1992; 117:1014-1015

8. Campbell NRC, Hasinoff BB, Stalts H, Rao B, Wong NCW: Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. Ann Intern Med 1992; 117:1010-1013

9. Sherman SI, Tielens ET, Ladenson PW: Sucralfate causes malabsorption of L-thyroxine. Am J Med 1994; 96:531-535

10. Burrow GN: Thyroid dysfunction in the recently pregnant: Postpartum thyroiditis. Thyroid 1994; 4:363-365

11. Rikabi AC, Young AE, Wilson C: Metastatic renal clear cell carcinoma in the thyroid gland diagnosed by fine needle aspiration cytology. Cytopathology 1991; 2:47-49

12. Green LK, Ro JY, Mackay B, Ayala AG, Luna MA: Renal cell carcinoma metastatic to the thyroid. Cancer 1989; 63:1810-1815

Editorials

Progress in Adult Acute Lymphoblastic Leukemia

ELSEWHERE IN this issue of THE WESTERN JOURNAL OF MEDICINE, Levitt and Lee provide an excellent review of the pathogenesis and treatment of acute lymphoblastic leukemia (ALL) in adults.[1] As noted by the authors, there has been considerable progress in our understanding of the nature of the malignant cell in ALL. The challenge we now face is the more difficult task of learning how to use this information.

One area where enormous progress has been made is in our understanding of the molecular events underlying adult ALL. In more than 90% of cases of ALL, a clonal chromosomal abnormality can be identified.[2] In about 25% of cases, the abnormality is one of numbers, with 20% of patients being hyperdiploid and 5% being hypodiploid. But more commonly, the abnormality is a specific chromosomal translocation. Such translocations are thought either to generate a novel gene (an oncogene) whose protein product acts on the host cell to induce characteristics of malignancy, or to cause a loss or an inactivation of genes whose proteins normally suppress cancer. In adult ALL, the genes involved in most of the commonly seen chromosomal translocations have now been identified.

The most common translocation found in adult ALL is the Philadelphia chromosome (Ph), t(9;22)(q34;q11). The Ph chromosome is formed by a translocation that fuses part of the *bcr* gene on chromosome 22 with sequences upstream of the c-*abl* proto-oncogene on chromosome 9. By traditional cytogenetic analysis, about 20% of adult ALL patients are Ph-positive. It has come as something of a surprise to find that at least an additional 10% of patients, Ph-negative by conventional cytogenetics, have *bcr-abl* rearrangements detectable with the use of polymerase chain reaction (PCR) assays.[3] This discrepancy is likely due either to the poor growth of lymphoid blasts, making conventional cytogenetic analysis difficult, or unusual "microscopic" translocations or "one-way" insertions of the *abl* gene into the *bcr* gene. The breaks in chromosome 22 occur in two limited regions, called the major and minor break-point cluster regions (BCRs). In chronic myelogenous leukemia, virtually all breaks are at the major BCR, giving rise to a p210 *bcr-abl* protein, but in patients with ALL, about 50% of cases occur in the minor BCR, giving rise to a p190 *bcr-abl* protein, the other 50% occurring at the major BCR. Despite the fact that we understand a great deal about t(9;22) in adult ALL, the only established therapeutic use of this knowledge to date has been as an important prognostic factor. When compared with Ph-negative adult ALL patients, patients with Ph-positive ALL have modestly lower complete remission rates and far shorter remission durations and, therefore, should be considered for allogeneic transplantation early in their disease course. Although results are still preliminary, patients with the minor break point may have a somewhat more aggressive disease than those with major break points. Polymerase chain reaction-based assays can be used to detect occult residual disease, but no clear clinical use of this approach has yet emerged.

The story for other translocations seen in adult ALL is similar. We now know the gene partners in most of these translocations, but we have as yet made little clinical use of the information. The identification of these translocations has in some cases provided us with additional prognostic information, and in those cases where specific primers are developed, a sensitive assay for minimal residual disease exists, but novel therapies have yet to emerge based on these studies. Other molecular abnormalities seen in adult ALL include mutations of N-*ras* in 10% to 25% of cases and mutations in Rb1 in a like percentage of patients. Mutations in p53 are rare in most forms of ALL, but common in patients with Burkitt's leukemia.

In addition to our increased knowledge of the molecular abnormalities seen in ALL, the immunophenotypic classification of adult ALL continues to be refined. This classification is based on increased knowledge about how normal cells acquire cell-surface antigens during development and information on the progression of events surrounding the rearrangements of immunoglobulin and T cell-receptor genes in normal cells. B-lineage ALL is now subdivided into at least four subtypes, including early pre-B common ALL antigen (CALLA)-positive and -negative ALL, pre-B ALL (note the absence of the "early"), and B-cell ALL. About 25% of cases are T-lineage ALL, including pre-T ALL and T-cell ALL. Cells from about 25% of cases of adult ALL coexpress the myeloid antigens CD13 or CD14 (or both). Similar to recent knowledge in the molecular events of ALL, advances in immunophenotyping have been used chiefly to refine the prognosis. Patients with T-cell and CALLA-positive, early pre-B ALL tend to do the best, whereas patients with pre-T ALL, CALLA-negative, early pre-B ALL, and those patients whose blasts coexpress myeloid antigens tend to do worse.[4,5]

Although the increased molecular and immunophenotypic information concerning adult ALL has not yet provided new therapies that can be considered established, a number of attempts are under way to try to make use of this information. The following examples are noted here:

- In those cases wherein the precise translocation leading to malignancy is known, it may be possible to silence the abnormal gene using antisense constructs or by eliminating the abnormal sequence using ribozymes.[6] Although antisense and ribozyme constructs work in vitro when a small number of cells are targeted, it is less certain whether the hurdle of having to deliver such therapy to every cell in vivo can be overcome. Thus, initial trials are looking at these agents as a way of treating marrow in vitro before autologous transplantation.

• In addition to silencing or eliminating the genetic defect in ALL, attempts are being made to use the defect to gain a therapeutic advantage. After exposure to DNA-damaging agents, normal cells undergo cell cycle arrest in either G1/S or G2/M, using the extra time to repair damage before progressing through the cell cycle. In many leukemia and lymphoma cell lines, the loss of p53 function leads to an inability to undergo cell cycle arrest or to trigger apoptosis, and thus these cells are relatively resistant to irradiation, but also rely entirely on G2/M arrest for DNA repair. Studies have recently shown that, at least in vitro, treatment during or after irradiation with agents that abolish G2/M arrest increase radiation sensitivity selectively in p53 mutant cells that rely on G2/M arrest without increasing the sensitivity of normal cells that can arrest in G1/S.[7,8]

• The immunophenotype of ALL may provide a target for therapy. Antibodies that recognize the specific antigens expressed by ALL can be used to target toxins to the leukemic cells. For example, human pre-B leukemia growing in immunodeficient mice has been successfully treated by targeting a tyrosine kinase inhibitor (genistein) to the B-cell–specific receptor CD19.[9] A slightly different approach has been undertaken in patients undergoing marrow transplantation for ALL. In these studies, antibodies against CD45, an antigen found on most hematopoietic cells, have been used to target iodine I 131 to sites of leukemia and normal marrow to more reliably eradicate the disease before marrow transplantation.[10]

• Following allogeneic transplantation for ALL, the risk of relapse is far less in patients in whom acute or chronic graft-versus-host disease develops than in identical twins or those free of graft-versus-host disease.[11] Studies in animals and humans have shown that the most likely explanation for this phenomenon is that cytotoxic T cells arising from the transplanted marrow recognize and react with HLA-minor antigens expressed either uniquely by leukemic cells (tumor-specific antigens) or shared by other cells of the same lineage (tumor-associated antigens). Studies under way at present are directed at identifying and isolating the T cells responsible for this outcome and their targets. Having the cells in hand would allow for their expansion and reinfusion, providing a form of tumor-specific adoptive immunotherapy. Identifying the T-cell target might lead to the generation of effective antitumor vaccines.

Although these approaches represent exciting new opportunities, it should be acknowledged that most of the advances made in the treatment of adult ALL have been the result of far more conventional sorts of studies. Based on these studies, 40% to 50% of adults with ALL can expect to be cured with the use of currently available therapies. Further progress will likely require both a continuation of conventional studies that look at new drug combinations, doses, and sequences and the introduction of some of the new approaches described earlier. To this end, it should also be remembered that ALL is a relatively uncommon disease and is, in fact, the least common of the four major leukemia categories. Thus, physicians should make every effort to include patients in established clinical trials to make sure that progress continues.

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REFERENCES

1. Levitt L, Lin R: Pathogenesis and treatment of adult acute lymphoblastic leukemia. West J Med 1996; 164:143-155

2. Williams DL, Raimondi S, Rivera G, George S, Berard CW, Murphy SB: Presence of clonal chromosome abnormalities in virtually all cases of acute lymphoblastic leukemia (Letter). N Engl J Med 1985; 313:640-641

3. Radich JP, Kopecky KJ, Boldt DH, et al: Detection of BCR-ABL fusion genes in adult acute lymphoblastic leukemia by the polymerase chain reaction. Leukemia 1994; 8:1688-1695

4. Hoelzer D, Thiel E, Löffler H, et al: Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 1988; 71:123-131

5. Boldt DH, Kopecky KJ, Head D, Gehly G, Radich JP, Appelbaum FR: Expression of myeloid antigens by blast cells in acute lymphoblastic leukemia of adults—The Southwest Oncology Group Experience. Leukemia 1994; 8:2118-2128

6. Szczylik C, Skórski T, Nicolaides NC, et al: Selective inhibition of leukemia cell proliferation by BCR-ABL antisense oligodeoxynucleotides. Science 1991; 253:562-565

7. Russell KJ, Wiens LW, Demers GW, Galloway DA, Plon SE, Groudine M: Abrogation of the G2 checkpoint results in differential radiosensitization of G1 checkpoint-deficient and G1 checkpoint-competent cells. Cancer Res 1995; 55:1639-1642

8. Powell SN, DeFrank JS, Connell P, et al: Differential sensitivity of p53(−) and p53(+) cells to caffeine-induced radiosensitization and override of G2 delay. Cancer Res 1995; 55:1643-1648

9. Uckun FM, Evans WE, Forsyth CJ, et al: Biotherapy of B-cell precursor leukemia by targeting genistein to CD19-associated tyrosine kinases. Science 1995; 267:886-891

10. Matthews DC, Appelbaum FR, Eary JF, et al: Development of a marrow transplant regimen for acute leukemia using targeted hematopoietic irradiation delivered by ^{131}I-labeled anti-CD45 antibody, combined with cyclophosphamide and total body irradiation. Blood 1995; 85:1122-1131

11. Sullivan KM, Weiden PL, Storb R, et al: Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. Blood 1989; 73:1720-1728

Correspondence

Microprocessor-Assessed Adherence With Once- or Twice-a-Day Dosing With Sulfonylurea—No Difference

To the Editor: The frequency of daily dosing is a factor that is assumed to influence a patient's compliance with therapy. Research is sketchy, however, and was done on small groups.[1] Pharmaceutical manufacturers promote products based on perceived advantages in the frequency of dosing; formulary decisions often are influenced by this aspect of medications.

One of the most commonly cited studies that found a difference between once- and twice-a-day dosing was retrospective in design and had a study population of three patients on once-a-day dosing and six patients on twice-a-day dosing.[2] In a review of 57 articles on the relationship between patient adherence and dosing frequency, the rate of compliance with once-a-day dosing (73%) was similar to that of twice-a-day dosing (70%).[3] In this review, drug classes varied from study to study, as did the method of assessing adherence, resulting in methodologic limitation affecting the conclusions. Although there is no gold standard for assessing adherence, the recent availability of an electronic medication-event monitoring system (MEMS, Aprex) allows objective quantitative adherence data to be collected.

In two separate research protocols assessing sulfonylurea compliance in patients with diabetes mellitus, we used a MEMS. The aim of both studies was to compare objective adherence data from MEMS with those of alternative methods in patients with non–insulin-dependent diabetes mellitus. We pooled data from 70 men with a mean age of 68 years (range, 41 to 82). Mean compliance for taking sulfonylurea for all patients was 85.58% ± 19%. A total of 40 patients were on once-a-day dosing, with a mean compliance of 89.6% ± 13.5%; 30 patients on twice-a-day dosing had a mean compliance of 81.3% ± 23.3%. This was not statistically different from the once-a-day dosing, using a separate variance estimate *t* test.

The clinical importance of the difference in adherence between once- and twice-a-day dosing varies with the drug. Missed sulfonylurea dosing may result in decreased metabolic control and an increased risk for complications of diabetes. Twice-a-day dosing may be preferable in terms of therapeutic efficacy because the consequences of a missed dose may be milder than with a once-a-day regimen.

The similar adherence between once- and twice-a-day dosing for sulfonylurea suggests that adherence should not be a factor that influences prescribing when making a decision regarding once- or twice-a-day use of sulfonylureas.

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REFERENCES

1. Haynes RB, Sackett DL, Taylor DN, Roberts R, Johnson A: Manipulation of the therapeutic regimen to improve compliance: Conceptions and misconceptions. Clin Pharmacol Ther 1977; 22:125-130

2. Gatley MS: To be taken as directed. J R Coll Gen Pract 1968; 16:39-44

3. Greenberg RN: Overview of patient compliance with medication dosing: A literature review. Clin Ther 1984; 6:592-599

Melanoma? Or Makeup?

To the Editor: In the Commentary in the July 1995 issue, Laurens P. White, MD, has taken up the question of a facial "lesion" in a well-known painting by Goya.[1] The painting is a group portrait of the royal family of Spain, done about 1800. White has concluded that the pigmented spot on the temple of the elder sister of King Carlos IV is a melanoma.

Gerald Hodge and I described Goya's depiction of the same subject and came to a different conclusion.[2] Large beauty marks were fashionable at the time Goya created this work. Goya also painted the king's wife, Queen Maria Luisa, with a similar "lesion" on her temple at least twice (see the exhibition catalogue that accompanied the Tokyo and Kyoto, Japan, Goya shows in 1971-1972, especially catalogue entries No. 5 and No. 27).

Is this pigmented "lesion" a melanoma, or is it makeup? Readers of The Western Journal of Medicine may wish to travel to Madrid to decide for themselves.

JAMES G. RAVIN, MD
3000 Regency Court, Ste 100
Toledo, OH 43623-3081

REFERENCES

1. White LP: What the artist sees and paints. West J Med 1995; 163:83-84

2. Hodge GP, Ravin JG: Spanish art—A contribution to medicine. JAMA 1969; 207:1693-1696

* * *

Dr White Responds

To the Editor: Regarding the thoughtful letter of J. G. Ravin, MD, about Goya's painting, my commentary included an illustration of an area of the large group painting of the family of King Charles IV. Ravin thinks that the large, irregular black area on the right temple of the Infanta Maria Josefa was a "beauty mark." It was my contention that this area was surely a lentigo maligna, probably with a melanoma. In the article that Ravin wrote with his colleague, G. P. Hodge they showed the preparatory painting of the Infanta and concluded that the irregular black area on her right temple was cosmetic.[1] They stated that such large "beauty marks" were commonly used by Goya and others, and they illustrated this by showing other paintings.

I recently reexamined both the preparatory portrait and the finished group painting in the Prado in Madrid. The black area in question is irregular in outline and measures nearly 4.5 cm in longest diameter and just over

3.0 cm across. I do not think it is a "beauty mark." I have seen the marks Ravin and Hodge described that were painted by Goya and others. They are regular, round or oval, and less than a tenth the size on the Infanta. I further think that raised edges can be seen around the black lesion on Maria Josefa.

Ravin is wise to raise the question of what Goya painted, as he and Hodge had done 26 years ago. I disagree with his interpretation, but he . . . is surely correct in urging readers to see the paintings for themselves in the finest museum in the world. While in Madrid, those interested might see one of the other paintings by Goya, which has a large "beauty mark" of about 1.0 cm on the face of Queen Maria Luisa.

LAURENS P. WHITE, MD
1580 Valencia St
San Francisco, CA 94110

REFERENCE

1. Hodge GP, Ravin JG: Spanish art—A contribution to medicine. JAMA 1969; 207:1693-1696

Correction

For the cover of the January 1996 issue, the electron micrograph of an Ebola virus was provided by C. J. Peters, MD.[1] To our readers who wondered about this before looking inside, we apologize.

THE EDITORS

REFERENCE

1. Peters CJ: Emerging infections—Ebola and other filoviruses. *In* Emerging and Reemerging Global Microbial Threats. West J Med 1996; 164:36-38

The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Consent

JESSICA DAVIDSON, MD, *Mountain View, California*

We all have at least one patient we'll never forget. Shelly was mine. I keep seeing her face in places where I never really saw her, out in the world. It's hard to imagine that sallow face lit up and laughing. When I met Shelly—26 years old, like me—I was shocked by her pallor, the dull look in her eyes, and the violence and relentlessness of her retching. Diabetes had never before looked like this to me, face drained of color, limbs almost flaccid with the lack of energy, eyes fixed on some distant point—of despair, I thought.

We couldn't help her, just watched day after day as she rose up from her pillows to grab her basin, and then fell back listless again. One day she went into diabetic ketoacidosis, and I ran in, intern fashion, to start the rescue, move her to the intensive care unit, take care of her. She said no. I couldn't believe what I was hearing. "But you'll die," I said. I think she raised her eyebrows, as if to say, "You think I don't know?"

She didn't die that time. We saved her without heroics. Next time, her mother, on a rare visit and looking tired, looked out the window, perhaps to where she'd rather be. Once, I was alone with Shelly and asked her if she wanted to live. Suddenly, there was such a look of light and hope on her face that I fought fiercely for her the next few times, despite her own despair, her family's palpable wish to be free, and her own body's traitorous refusal to stay alive. She couldn't keep the ketoacidosis away for more than a day, or we couldn't keep it from her. Finally, bullied on all sides, by her mother's loud talking about Palm Springs, by my resident who was bored with a case that was going nowhere, by the head nurse who resented the demands on her staff—and thinking that it was probably useless to try, anyway—I gave in and let her die. She wanted to die, she said, and looked to the wall. I pushed away the other look, the one that showed what neither of us could bear. Four days later, my resident videotaped her autopsy, and there was no going back.

I had read about that look and what was behind it, before I had become a "medical" person and before I had ever actually seen it in the eyes of someone lying in a bed in front of me. I had not yet felt that way myself, not having been near death, but reading Katherine Anne Porter's "Pale Horse, Pale Rider," I had my first glimpse of what it might feel like to be on the brink between a hellish life and the release of death, and still wish for life. Porter wrote about Miranda, a young reporter in the time of the First World War, who was desperately ill with influenza and fighting, as if in a dream, her way back to life:

> She lay on a narrow ledge over a pit that she knew to be bottomless, though she could not comprehend it. . . . I shall not know when it happens, I shall not feel or remember, why can't I consent now, I am lost, there is no hope for me. Look, she told herself, there it is, that is death and there is nothing to fear. But she could not consent, still shrinking stiffly against the granite wall that was her childhood dream of safety, breathing slowly for fear of squandering breath, saying desperately, Look, don't be afraid, it is nothing, it is only eternity.[1(p310)]

This might as well have been Shelly. She was lost and could not be saved. There was nothing to hope for—hope was for other young women, who lived out there, whose every minute was not a misery—and yet, incredibly, she did hope, with a fierceness I did not understand until it was too late. Shelly consented finally, but only out loud. Inside, I am sure now, she was shrinking as unbelievingly as Miranda from this end of herself, this nothing. Miranda in the story finally wakes up to the sounds of Armistice Day. She says, "Please open the window, please, I smell death in here."[1(p313)] For Shelly, there was no airing out the lingering smell of death from her life. Wanting life that badly does not mean that you can have it. But at least, I think, next time I will not turn away from seeing that hope on someone's face. I will not let myself be consoled by a consent I know is not there.

REFERENCE

1. Porter KA: Pale horse, pale rider, *In* The Collected Stories of Katherine Anne Porter. New York, NY, New American Library, 1970

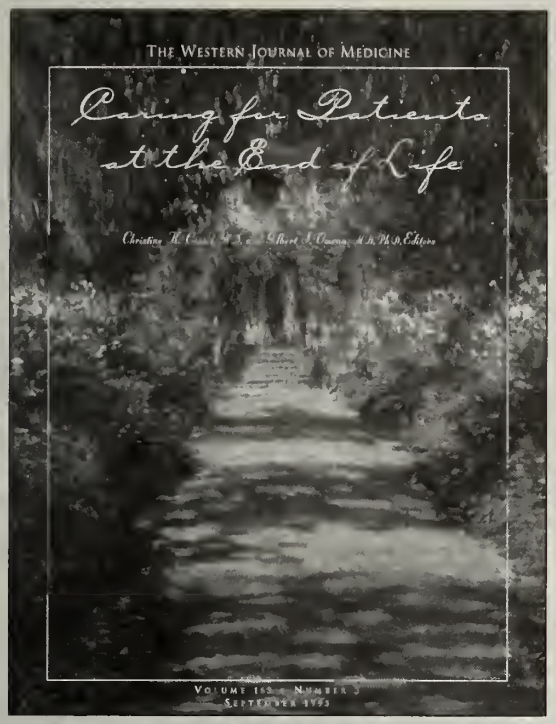
* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Davidson J: Consent. West J Med 1996; 164:184)

Dr Davidson is an internist in Milpitas, California.
Reprint requests to Jessica Davidson, MD, 2250 Latham St, No. 39, Mountain View, CA 94040.



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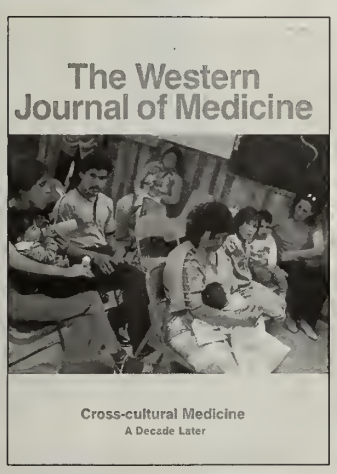

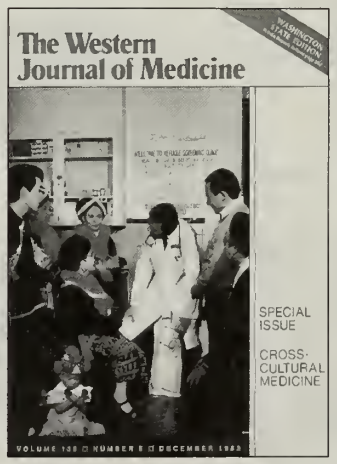

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Special Issue Editor, 1983

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Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, New Mexico Medical Society Offices, Albuquerque.

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Black and Older Hypertensives Are Similar, Yet Different...

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- Pathophysiology[1-3]
- Concomitant conditions[2-5] and
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INDICATION AND USAGE: ADALAT CC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS: Known hypersensitivity to nifedipine.

WARNINGS: Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.
Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.
Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.
Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.
Congestive Heart Failure: Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).
Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.
Information for Patients: ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.
Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.
Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.
Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.
Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.
Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS).
ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.
Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.
Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.
Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).
Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.
Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m^2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.
The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.
There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EXPERIENCES: The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.
The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.
Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).
Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.
The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:
Body as a Whole/Systemic: chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency
Other adverse events reported with an incidence of less than 1.0% were:
Body as a Whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiertases **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement
The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to each patient's needs. It is recommended that ADALAT CC be administered orally once daily on an empty stomach. ADALAT CC is an extended release dosage form and tablets should be swallowed whole, not bitten or divided. In general, titration should proceed over a 7-14 day period starting with 30 mg once daily. Upward titration should be based on therapeutic efficacy and safety. The usual maintenance dose is 30 mg to 60 mg once daily. Titration to doses above 90 mg daily is not recommended.
If discontinuation of ADALAT CC is necessary, sound clinical practice suggests that the dosage should be decreased gradually with close physician supervision.
Care should be taken when dispensing ADALAT CC to assure that the extended release dosage form has been prescribed.

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References:
1. Messerli FH. Management of Essential Hypertension in the Black Patient: Profiling as the Initial Approach to Treatment. *J Natl Med Assoc.* 1989;81(1):17-23. **2.** Blake GH. Primary Hypertension: The Role of Individualized Therapy. *Am Fam Physician.* 1994;50(1):138-146. **3.** Weart CW, Weber MA, Weinberger MH. Which drug for the aging hypertensive? *Patient Care.* 1992;26:215-257. **4.** Murphy MB. Selecting Optimum Antihypertensive Therapy: Indications for Choosing a Calcium Channel Blocker. *Am J Med.* 1992;93(Suppl 2A):2A-38S through 2A-44S. **5.** Opie LH. Calcium Channel Antagonists (Calcium Entry Blockers) and Kaplan NM, Opie LH. Antihypertensive Drugs. In: Opie LH, ed. *Drugs for the Heart.* 3rd ed. Philadelphia, PA: W. B. Saunders Company;1991:42-73, 155-179. **6.** Data on file, Bayer Corporation, Pharmaceutical Division. **7.** Glasser SP, Ripa SR, Allenby KS, Schwartz LA, Commins BM, Jungerwirth S, on behalf of the Nifedipine Study Group. The Efficacy and Safety of Once-Daily Nifedipine Administered without Food: The Coat-Core Formulation Compared with the Gastrointestinal Therapeutic System Formulation in Patients with Mild-to-Moderate Hypertension. *Clin Ther.* 1995;17(2):296-312. **8.** Feig PU, Gibson L, MacCarthy EP, Pettis PP, Schwartz L, the Adalat® CC Cooperative Study Group. The Efficacy and Safety of Once-Daily Nifedipine Coat-Core in the Treatment of Mild-to-Moderate Hypertension. *Curr Ther.* 1993;15(6):963-975. **9.** Adalat® CC Product Monograph, April 1995. **10.** *Redbook Update.* Montvale, NJ, Medical Economics Data, Inc., January 1996.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

April 1-3—**Management Strategies in Complex Congenital Heart Disease.** Mayo Foundation at the Point Squaw Peak, Phoenix. Mon-Wed. Contact: (800) 323-2688.

April 9-13—**New Frontiers in Pain.** Maricopa Medical Center at the Radisson Resort Hotel, Scottsdale. Tues-Sat. Contact: Beverlee Anderson, (602) 267-5366.

April 10-13—**21st Annual Primary Care Update.** University of Arizona College of Medicine at the Tucson Hilton East, Tucson. Wed-Sat. Contact: U of A.

April 18-20—**Upper Extremity Trauma and Reconstructive Surgery.** Mayo Foundation at The Pointe Hilton Resort, Phoenix. Thurs-Sat. Contact: (800) 323-2688.

April 22-25—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920.

April 28-May 1—**Southwest Surgical Congress—Annual Meeting.** Marriott's Camelback Inn Resort and Golf Club, Scottsdale. Sun-Wed. Contact: (312) 527-6667.

May 4—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale, Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

May 6-10—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

May 9-10—**Vascular Access for Hemodialysis V, Ultrasonography Assessment, OST Consideration, Stents, Graphs Lysis.** Ohio State University Medical Center at the Westin La Paloma, Tucson. Thurs-Fri. Contact: (708) 550-0090.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale. (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

CARDIOLOGY

April 13-14—**Practical Advances in Vascular Disease.** Medical Education Collaborative at Loews Coronado Bay Resort, San Diego. Sat-Sun. 10 hrs. $125. Contact: Medical Education Collaborative, 137 W Jewell Ave, Ste 251, Lakewood, CO 80228. (800) 442-6632.

April 25-27—**Sixth Annual Symposium on Coronary Stenting.** Scripps Clinic & Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. Contact: Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

June 5-8—**Advanced Echocardiography and Doppler Ultrasound 1996.** American College of Cardiology at Hyatt Islandia, San Diego. Wed-Sat. 23.5 hrs. Contact: ACC, Registration Secretary, Extramural Programs Dept, Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

June 28-30—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

DERMATOLOGY

June 7-9—**3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at UCSF. Fri-Sun. Contact: UCSF.

October 12-13—**The Skin From A To Z: Tips on Practical and Office Techniques.** UCSF at UCSF. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

May 14-15—**7th Annual High Risk Emergency Medicine.** American College of Emergency Physicians at Hyatt at Fisherman's Wharf, San Francisco. Tues-Wed. 15 hrs. $299 to $499. Contact: Alpen Meeting Service, (800) 451-RISK.

May 31-June 6—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. 18 hrs. $250. Contact: USC.

June 20—**Cost Effective Emergency Medicine.** American College of Emergency Physicians at The Mirage, Las Vegas. Thurs. 8 hrs. $199-$249. Contact: Alpen Meeting Services, (800) 451-RISK.

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency La Jolla, San Diego. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

ENDOCRINOLOGY/METABOLISM

June 7-11—**Molecular Steriodogenesis.** UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

EPIDEMIOLOGY/INFECTIOUS DISEASE

May 1-3—**17th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17.5 hrs. $410. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

April 1-4—**Primary Care in Paradise: Maui 1996.** Scripps Clinic and Research Foundation at Embassy Suites Resort, Kaanapali Beach, Maui, Hawaii. Mon-Thurs. 16 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 6-13—**Sixth Kaiser Permanente National Conference on Musculoskeletal Medicine.** Kauai Marriott Resort, Kauai, Hawaii. 29 hrs. $400. Contact: Ferdy Massimino, MD, 200 Muir Rd, Martinez, CA 94553. (510) 372-1457.

April 7-12—**Ninth Annual Primary Care Medicine: Update 1996.** UCSF at Intercontinental Resort, Maui, Hawaii. Sun-Fri. 20 hrs. $595. Contact: UCSF.

April 13—**The Team Approach to Oncology: The Primary Care Physician's Role.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6.5 hrs. $95. Contact: UCD.

April 18-21—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hilton Beach & Tennis Resort, San Diego. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 27-May 1—**29th Society of Teachers of Family Medicine Annual Spring Conference.** AAFP and Society of Teachers of Family Medicine at the Hyatt Regency at Embarcadero Center, San Francisco. Sat-Wed. Contact: Ray Rosetta, Director of Meetings and Programs, The Society of Teachers of Family Medicine. (800) 274-4512.

May 17-21—**Essentials in Primary Care.** Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 7-9—**9th Annual Medical Office Laboratory Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego. Fri-Sun. 23 hrs. $475. Contact: Nancy Geiser, College of Extended Studies. (619) 594-6255.

June 10-12—**2nd Annual Sports and Occupational Medicine in Primary Care: From Prevention to Treatment Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego, Mon-Wed. 20 hrs. $475. Contact: Nancy Geiser, College of Extended Studies. (619) 594-6255.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

Announcing the Spring 1996 CME Category 1 Program

CME At Good Sam

Don't Miss These Outstanding Educational Opportunities!

Good Samaritan Hospital, Los Angeles is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. For further information, contact Physician Education Services/ CME at 1225 Wilshire Blvd., Los Angeles, CA 90017. Please call (213) 977-2335 or fax request to (213) 977-2333.

Good Samaritan Hospital
Los Angeles

- *March 12 AND May 14, 6:30 PM-10 PM*
  LA Cardiology Society Evening Forum
  David S. Cannom, M.D., Course Director
- *March 16, 8:30 AM-6:15 PM*
  Retina Update 1996 Symposium
  David S. Boyer, M.D., Roger L. Novack, M.D., Ph.D., & Edgar L. Thomas, M.D., Course Directors
- *March 18, 6 PM-8:15 PM*
  Radiation Oncology Evening:
  Management of Early Stage Breast Cancer
  David P. Winchester, M.D., Guest Speaker
  Rufus Mark, M.D., Course Director
- *March 20, 3:30 PM-8:45 PM*
  Epilepsy: *New Directions, New Solutions*
  William W. Sutherling, M.D., Course Director
- *April 19, 8:30 AM-6 PM*
  Echocardiography Board Review Course:
  4th Annual Echo Conference
  Charles Pollick, M.D., Course Director
- *May 3, 8 AM-4 PM*
  Controversies in Cardiovascular Intervention
  Ray V. Matthews, M.D., Course Director
- *May 8, 5:30-7:30 PM*
  The Helen Ford Memorial Oncology Lecture:
  Genetics Risk Assessment for Cancer
  Mary Daly, M.D., Guest Speaker
  Lowell Irwin, M.D., Course Director
- *May 15, 5:30 PM-8 PM*
  Neuroscience Quarterly Evening Lecture:
  Functional Neurosurgery– Past, Present, and Future
  Dean "Skip" Jacques, M.D., Course Director

June 28-30—**San Diego Academy of Family Physicians' 40th Annual Postgraduate Symposium—Family Medicine Update: 1996.** San Diego Academy of Family Physicians at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-$300. Contact: Terry Camarata. (619) 422-1186.

August 2-4—**Managing Respiratory Diseases.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

August 2-4—**Cardiology for the Primary Care Physician.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 5-7—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Doubletree Hotel, Monterey. Fri-Mon. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

INTERNAL MEDICINE

April 11-13—**Recent Advances in Hematopoietic Stem Cell Transplantation.** UCSD at Hilton Beach & Tennis Resort, San Diego. Thurs-Sat. Contact: UCSD.

April 20—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 6 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-6310.

May 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims.** UCSD at Hilton Beach & Tennis Resort, San Diego. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

September 27-October 2—**Internal Medicine 1996—Fall Program.** Continuing Medical Education Associates at Loews Coronado Bay Resort, San Diego. Fri-Wed. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

NEPHROLOGY

August 2-8—**12th Comprehensive Nephrology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Thurs. 50 hrs. $800. Contact: UCLA.

ONCOLOGY

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

April 13—**The Team Approach to Oncology: The Primary Care Physician's Role.** UCD at Cancer Center Auditorium, Sacramento. Sat. 6.5 hrs. $95. Contact: UCD.

OPHTHALMOLOGY

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037 (619) 554-8556.

OTOLARYNGOLOGY

May 23-25—**Vestibular Adaptation.** UCLA at Miramar Sheraton Hotel, Santa Monica. Thurs-Sat. 17 hrs. $400. Contact: UCLA.

June 22-28—**1995-1996 Skull Base Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles 90057.

June 29-July 4—**Second International Skull Base Congress and the Seventh Annual Meeting of the North American Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Floor, Los Angeles 90057.

July 5-7—**Current Concepts in Allergy and Otolaryngology.** Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital, Continuing Medical Education Office, 3020 Children's Way, Room 5021, San Diego 92123. (619) 576-4072.

PATHOLOGY

April 1-5—**Diagnostic Approaches to Lymphoproliferative Disorders.** Scripps Clinic and Research Foundation at Ritz-Carlton, Maui, Hawaii. Mon-Fri. 26 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 23-25—**Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

PEDIATRICS

April 21-23—**Weaning '96.** USC at Stouffer Renaissance Esmeralda Resort, Palm Springs. Sun-Tues. 10 hrs. $525. Contact: USC.

May 16-18—**29th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 16 hrs. $350. Contact: UCSF.

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians.** UCSD at Hilton Beach & Tennis Resort, San Diego. Thurs-Sat. 15 hrs. $350. Contact: UCSD.

PLASTIC SURGERY

June 7-9—**The 3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at UCSF. Fri-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

April 19-21—**West Coast Neuropsychology Conference.** UCSD at Pan Pacific Hotel, San Diego. Fri-Sun. 15.5 hrs. $325. Contact: UCSD.

May 22-24—**3rd Annual Sexual Assault Response Team (SART) Training.** UCD at Red Lion Hotel, Sacramento. Wed-Fri. 19 hrs. $160. Contact: UCD.

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS. (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, 92037. (619) 554-8556.

RADIOLOGY

April 6—**UCSD Spring Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Sat. 6.25 hrs. $135. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 7-12—**UCSD Neuro and Musculoskeletal MR Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 7-12—**UCSD 16th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $695. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

April 12-14—**UCSD Breast Imaging & Interventions Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 15 hrs. $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, San Diego. Sat-Thurs. 22.5 hrs. $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925 (770) 641-9773.

August 15-18—**Minimally Invasive Therapy of the Brain.** UCSD at Ritz-Carlton Hotel, Marina del Rey. Thurs-Sun. 20 hrs. $495. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 14 hrs. $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

April 25-27—**The Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

June 26-29—**13th Annual San Diego Shoulder Orthroscopy Meeting.** Tri City Medical Center at Hyatt Regency, La Jolla. Wed-Sat. 24 hrs. $1,375. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD at San Diego. Mon-Sat. 36 hrs. $1,395. Contact: UCSD.

UROLOGY

April 25-28—**5th Annual Spring Clinical Nephrology Meetings.** National Kidney Foundation at Disneyland Hotel, Anaheim. Thurs-Sun. 26 hrs. Contact: National Kidney Foundation, Donna Fingerhut. (800) 622-9010.

GENERAL/MULTIDISCIPLINARY

April 27-29—**5th Annual Pain Conference: Primary Care Overview of Pain Management.** UCD at Tenaya Lodge at Yosemite, Fish Camp. Sat-Mon. Contact: UCD.

May 31-June 2—**38th Annual Scientific Meeting of the American Association for the Study of Headache.** San Diego. Fri-Sun. Contact: AASH. (619) 845-1720.

August 8-11—**38th Annual Postgraduate Refresher Course—Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 6-8—**National Stroke Meeting: The Clinical Aspects of Stroke Diagnosis and Treatment.** Medical Education Resources at Red Lion Hotel and Conference Center, Colorado Springs. Thurs-Sat. Contact: Jaclynna Williams. (303) 798-9683. FAX (303) 798-5731.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline. (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists. (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospitals at St Anthony Hospital, Denver. Contact: Rose Powell. (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe, Santa Fe. Thurs-Sun. Contact: UNM SOM.

July 11-14—**New Choices, New Challenges, Psychopharmacology in the Primary Care Setting.** La Fonda Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**Podiatric Surgical Seminar.** Hotel Santa Fe, Santa Fe. Wed-Thurs. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**How to Diagnose and Treat Arrhythmias for the Primary Care Physician.** Eldorado Hotel, Santa Fe. Wed-Sun. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

August 2-4—**Practical Pediatrics.** La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 15-18—**Primary Care for the Aging Person.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 22-25—**Implementing Change in Patient Behavior and Clinical Practice.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 3-6—**Building "Virtual" Integrated Delivery Systems: Thriving in an Advanced Healthcare Market.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

June 23-24—**Otolaryngology in the Intermountain West**. University Park Hotel, Salt Lake City. Sun-Mon. 5 hrs. $50. Contact: UUSM.

July 13-20—**Update in Clinical Microbiology and Immunology**. Snow King Resort at Jackson Hole, Wyoming. Sat-Sat. 25 hrs. Contact: UUSM.

August 9-10—**Advanced Obstetrical Life Support**. University Park Hotel, Salt Lake City. 24 hrs. $450. Contact: UUSM.

August 12-16—**Northwest Neuroradiology and Advanced MR Imaging Course**. Pan Pacific Hotel, Vancouver, British Columbia. Mon-Fri. 42 hrs. $1,250. Contact: UUSM.

September 20—**Ophthalmology: Clinical Faculty Day**. Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological**. University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

October 7-9—**Preconference Workshop**. Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging**. University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

MEDICAL GRAND ROUNDS

March 28-30—**4th International Congress on Alport Syndrome.** University Park Hotel, Salt Lake City. Contact: UUSM.

April 27—**Advances in the Management of Pain in the Acute and Chronic Settings.** University Park Hotel, Salt Lake City. 6 hrs. Contact: UUSM.

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

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Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 1-5—**CME at Maui.** Kapalua, Maui, Hawaii. Mon.-Fri. Contact: Pierce County College of Medical Education. (206) 627-7137.

April 3-5—**Occupational Hazards to Health Care Workers.** Seattle. Wed-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

April 19—**Sixth Annual Health Education Conference: New Practice Models: Integrating Patient & Health Education in a Clinical Setting.** Seattle. Fri. Contact: Providence/Seattle Medical Center. (206) 320-2552.

April 19-20—**Surgical Update 1996.** Pierce County College of Medical Education, Tacoma. Fri-Sat. Contact: PCMS CME.

April 26—**Cardiology for Primary Care.** Pierce County College of Medical Education, Tacoma. Fri. Contact: PCMS CME.

May 2—**Pesticide Medicine.** Yakima. Thurs. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

May 9—**Hypertension.** Seattle. Thurs. Contact: U/W.

May 16—**Women's Health Care.** Seattle. Thurs. Contact: Providence/Seattle Medical Center. (206) 320-2552.

May 31—**Infectious Diseases Update.** Seattle. Fri. Contact: U/W.

June 7—**Nuts, Bolts, and Innovation in Gastrointestinal Disease III.** Pierce County College of Medical Education, Tacoma. Fri. Contact: PCMS CME.

June 12-14—**4th Annual Pacific Northwest Cardiovascular Symposium.** Seattle. Wed-Fri. Contact: Providence/Seattle Medical Center. (206) 320-2552.

June 20-21—**ACLS.** Pierce County College of Medical Education, Tacoma. Thurs-Fri. Contact: PCMS CME.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

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U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

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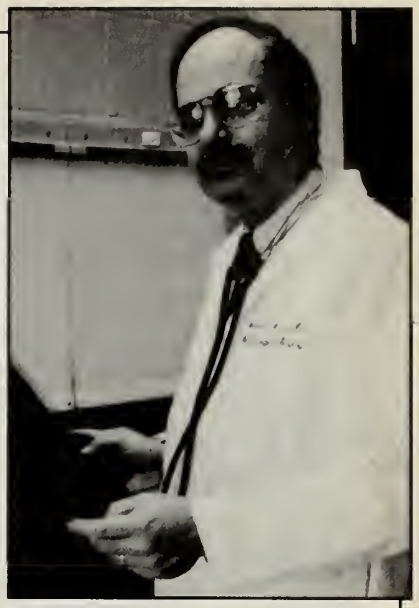

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California Medical Association

Beck, Frederick, Oakland. Died Jan 12, 1996, aged 90. Graduate of University of Nebraska College of Medicine, Omaha, 1935. Licensed in California in 1940. Dr Beck was a member of the Alameda-Contra Costa Medical Association.

Berg, John A., Sacramento. Died Jan 20, 1996, aged 81. Graduate of St. Louis University School of Medicine, Missouri, 1940. Licensed in California in 1940. Dr Berg was a member of the Sacramento-El Dorado Medical Society.

Chicarino-Netto, Jose, Fairfield and Vacaville. Died Feb 14, 1996, aged 68. Graduate of University Federal De Rio De Janeiro, Brazil, 1954. Licensed in California in 1966. Dr Chicarino-Netto was a member of the Solano County Medical Society.

Gallagher, Raymond C., Oakland. Died Aug 13, 1995, aged 70. Graduate of University of Wisconsin Medical School, Madison, 1948. Licensed in California in 1949. Dr Gallagher was a member of the Alameda-Contra Costa Medical Association.

Grigorieff, Paul A., Eureka. Died Nov 7, 1995, aged 76. Graduate of University of California, San Francisco, School of Medicine, 1944. Dr Grigorieff was a member of the Humboldt-Del Norte Medical Society.

Griswold, Robert L., Stockton. Died Dec 22, 1995, aged 71. Graduate of Case Western Reserve University School of Medicine, Cleveland, Ohio, 1949. Licensed in California in 1951. Dr Griswold was a member of the San Joaquin County Medical Society.

Hanberry, John W., Stanford. Died Jan 14, 1996, aged 76. Graduate of Stanford University School of Medicine, California, 1945. Dr Hanberry was a member of the Santa Clara County Medical Association.

Hebert, Frederick, Berkeley. Died Jan 17, 1996, aged 78. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1943. Licensed in California in 1944. Dr Hebert was a member of the Alameda-Contra Costa Medical Association.

Hogle, Glen S., Santa Ana. Died Jan 15, 1996, aged 74. Graduate of University of Cincinnati College of Medicine, Ohio, 1951. Licensed in California in 1959. Dr Hogle was a member of the Orange County Medical Association.

Judd, Richard W., San Bernadino. Died Oct 19, 1995, aged 84. Graduate of Medical College of Wisconsin, Milwaukee, 1939. Licensed in California in 1946. Dr Judd was a member of the San Bernadino County Medical Society.

Levy, Edward I., San Diego. Died Sep 15, 1995, aged 89. Graduate of University of California, San Francisco, School of Medicine, 1932. Dr Levy was a member of the San Diego County Medical Society.

Metheny, John A., Oakland. Died Aug 24, 1995, aged 64. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1956. Licensed in California in 1957. Dr Metheny was a member of the Alameda-Contra Costa Medical Association.

Nakashima, Donald, Lodi. Died Jan 25, 1996, aged 72. Graduate of University of Nebraska College of Medicine, Omaha, 1951. Licensed in California in 1953. Dr Nakashima was a member of the San Joaquin County Medical Society.

Necker, Elmer, Lodi. Died Dec 21, 1995, aged 69. Graduate of Loma Linda University of School of Medicine, California, 1955. Dr Necker was a member of the San Joaquin County Medical Society.

Pouteau, Gallerand G., Napa. Died Dec 3, 1995, aged 71. Graduate of University of Oregon Medical School, Portland, 1947. Licensed in California in 1948. Dr Pouteau was a member of the Napa County Medical Society.

Preston, Frederick W., Santa Barbara. Died Feb 2, 1996, aged 83. Graduate of Northwestern University Medical School, Chicago, Illinois, 1940. Licensed in California in 1975. Dr Preston was a member of the Santa Barbara County Medical Society.

Reavis, James, Yountville. Died Nov 22, 1995, aged 82. Graduate of University of California, San Francisco, School of Medicine, 1943. Dr Reavis was a member of the Napa County Medical Society.

Ripple, Richard C., Sacramento. Died Jan 13, 1996, aged 79. Graduate of University of Nebraska College of Medicine, Omaha, 1945. Licensed in California in 1950. Dr Ripple was a member of the Sacramento-El Dorado Medical Society.

Rubin, Milton R., Fresno. Died Jan 22, 1996, aged 85. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1934. Licensed in California in 1951. Dr Rubin was a member of the Fresno-Madera Medical Society.

Shenson, Ben, San Francisco. Died Aug 15, 1995, aged 79. Graduate of Stanford University School of Medicine, California, 1940. Dr Shenson was a member of the San Francisco Medical Society.

Sitney, J. Jay, San Jose. Died Aug 20, 1995, aged 81. Graduate of Columbia University College of Physicians and Surgeons, New York, 1938. Licensed in California in 1943. Dr Sitney was a member of the Santa Clara County Medical Association.

Thayer, Thomas, Fresno. Died Jan 19, 1996, aged 60. Graduate of University of California, Los Angeles, School of Medicine, 1961. Dr Thayer was a member of the Fresno-Madera Medical Society.

Wolohan, Jeremiah, Alameda. Died Jan 18, 1996, aged 78. Graduate of Stanford University School of Medicine, Palo Alto, California, 1944. Dr Wolohan was a member of the Alameda-Contra Costa Medical Association.

Denver Medical Society

Guese, Raymond F., Denver. Died Jan 3, 1996, aged 73. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1948. Licensed in Colorado in 1954. Dr Guese was a member of the Denver Medical Society.

Wyoming Medical Society

Gramlich, John B., Cheyenne. Died Oct 9, 1995, aged 80. Graduate of Columbia University College of Physicians and Surgeons, New York, 1939. Licensed in Wyoming in 1946. Dr Gramlich was a member of the Laramie County Medical Society.

Biomedical Science

Thrombopoietin and Platelet Development

KENNETH KAUSHANSKY, MD, *Seattle, Washington*

Blood cell production, termed hematopoiesis, is a complex process dependent on bone marrow stromal cells, polypeptide growth factors, and primitive stem and progenitor cells.[1,2] Pioneering work in the early and mid-1960s suggested that marrow contains undifferentiated cells that develop into the mature blood elements.[3-5] Over the ensuing 30 years, a number of soluble and membrane-bound polypeptides have been characterized that support the survival, proliferation, and differentiation of primitive marrow cells into erythrocytes, neutrophils, eosinophils, basophils, monocytes or macrophages, and lymphocytes. Nearly all of these molecules have been cloned.

In more recent years, the availability of these recombinant cytokines and purified hematopoietic progenitors has led to the concept that stem cells are supported by two types of growth factors, one that acts on several types of primitive progenitor cells and one that acts specifically on a single lineage late in its developmental pathway. For example, erythrocyte development is thought to be supported by the early action of stem cell factor (also called steel factor, kit ligand, and mast cell growth factor)[6] and erythropoietin, which acts to induce the terminal phases of erythrocyte development.[7] For neutrophils, interleukin (IL) 3 or granulocyte-macrophage colony-stimulating factor (CSF) and granulocyte (G)-CSF appear to fill these early and late supportive roles.[8-10] Many of these cytokines, especially the late-acting hormones erythropoietin and G-CSF, have found important clinical roles in the stimulation of erythrocyte and leukocyte production in states of natural and iatrogenic marrow failure.[11,12] Unfortunately, the cytokines responsible for megakaryocyte and platelet development have been more difficult to identify.

In the late 1960s and early 1970s, several investigators showed that the plasma of thrombocytopenic animals contained a substance that induced an increased uptake of selenium 75- or sulfur 35-labeled methionine into the platelets of normal recipients, a process thought to represent new platelet production. This substance was called "thrombopoietin" and appeared to support the late stages of megakaryocyte maturation.[13,14] The marrow of recipient animals was characterized by increases in megakaryocyte size and polyploidy, rather than by changes in cell number. Despite this early progress, the subsequent steps of biochemical purification and cloning of thrombopoietin proved elusive. Using in vivo assays or surrogate in vitro methods, several investigators in the mid-1980s were able to partially purify a thrombopoietic material from thrombocytopenic plasma.[15-18] Such preparations could recapitulate in vivo findings; the partially purified material induced megakaryocyte ploidy and cytoplasmic maturation in suspension cultures of rodent megakaryocytes. Unfortunately, none of these studies led to a purification of thrombopoietin sufficient to provide the amino acid sequence.

By adapting many of the techniques useful for myeloid and erythroid cell culture, several investigators established that megakaryocyte production could be supported in serum or plasma containing cultures by IL-3[19] and to a lesser extent by stem cell factor.[20] Both of these cytokines appeared to act early in the developmental process; cell numbers were increased, but in the absence of plasma, megakaryocytes failed to mature. These results suggested that IL-3 or stem cell factor (or both) was the early acting factor(s) for megakaryocyte development, but that plasma contained a distinct substance responsible for megakaryocyte maturation.[21] These conclusions were consistent with results from studies of plasma thrombopoietin. Despite this greater understanding of the characteristics of megakaryocyte and platelet development, investigators were no further along in cloning a distinct thrombopoietin. Many in the field began to think that if modern technology could not clone it, it did not exist.

In the late 1980s and early 1990s, several cytokines were identified that displayed pleotropic biologic activities including effects on megakaryocyte production. Interleukins 6 and 11 and leukocyte inhibitory factor all were shown to augment megakaryocyte formation in response to IL-3 or stem cell factor.[22-24] Moreover, these cytokines appeared to affect megakaryocyte maturation, causing increases in cell size and ploidy both in vitro and in vivo. Although it was clear that neither IL-6 nor IL-11 was the thrombopoietic substance identified in plasma,[25,26] many in the field began to think that together these pleotropic cytokines might play the role of a thrombopoietin, further reinforcing the growing suspicion that a distinct lineage-specific megakaryocyte maturation factor did not exist. If so, however, megakaryocyte and

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ABBREVIATIONS USED IN TEXT

CSF = colony-stimulating factor
G-CSF = granulocyte colony-stimulating factor
IL = interleukin

platelet development was organized in a far different way from erythrocyte or leukocyte production.

Occasionally in science, findings from one field, although interesting and important in their own right, have a profound catalytic effect on a seemingly unrelated area of research. Work with the murine retrovirus MPLV had such an effect on megakaryocytopoiesis. In the late 1980s, a retroviral complex was described that induced an acute myeloproliferative syndrome in recipient mice.[27] In 1990 the transforming gene responsible for the disease was identified,[28] and the corresponding human proto-oncogene, c-*mpl*, cloned from human erythroleukemia cells in 1992.[29] On the basis of spatially conserved cysteine residues and a pentapeptide juxtamembrane sequence, features characteristic of a large number of growth factor receptors,[30] it was suggested that c-*mpl* encoded a cytokine receptor. The ligand for the polypeptide was not known, however; c-*mpl* encoded an orphan receptor.

Based on its cell of origin, a biphenotypic leukemia that can be induced to display megakaryocytic features,[31] we and others hypothesized that c-*mpl* might encode the thrombopoietin receptor. On this basis, many groups sought to clone its ligand. Additional data emerged suggesting that this hypothesis was correct. First, c-*mpl* expression appeared to be limited to normal megakaryocytes, their precursors, or their progeny.[29,32] When a group of leukemic cell lines was surveyed for c-*mpl* expression, only those that displayed characteristics of the megakaryocytic lineage were found positive.[32] Next, genetic engineering of a hybrid receptor composed of the IL-4–receptor extracellular domain and the intracellular domain of c-*mpl* functioned to transmit a proliferative signal in a leukemic cell line.[33] This result confirmed that c-*mpl* encoded a growth-promoting receptor. But the strongest evidence that c-*mpl* and its ligand functioned in megakaryocyte development came from studies in which c-*mpl* expression was interrupted. By using antisense deoxyoligonucleotides, investigators showed that megakaryocytic, but not erythroid or myeloid, development of highly selected marrow progenitor and stem cells was markedly reduced if c-*mpl* expression was inhibited.[34] With these data as further validation of the hypothesis, work progressed at a frantic pace. Within two years of the cloning of c-*mpl*, five separate groups, using at least three distinct strategies, reported the sequence of the mpl ligand.[35-39] The recombinant protein displayed all of the activities proposed for thrombopoietin.

Using the murine protein, we were able to show that the mpl ligand increased megakaryocyte size, ploidy, and surface membrane expression of platelet-specific glycoproteins.[40] Moreover, when administered to normal mice, the protein substantially increased the number of marrow and splenic megakaryocytic progenitors, megakaryocytes, and peripheral blood platelets.[35,40] Qualitatively similar results have been reported using the human homologue.[36,37,39] Other workers demonstrated that levels of the plasma mpl ligand were inversely related to platelet mass,[41] a finding later confirmed and extended by others.[42,43] Although thrombopoietin was not originally thought to stimulate the proliferation of megakaryocytic progenitor cells, the mpl ligand was found to be a potent stimulus of megakaryocyte colony formation. More recently, the elimination of c-*mpl* expression in genetically engineered mice and studies using a soluble, neutralizing form of the receptor have shown that thrombopoietin is essential for normal megakaryocyte and platelet development.[44,45] Together these findings clearly establish that the mpl ligand is identical to plasma thrombopoietin. To paraphrase Descartes, "It has been cloned; therefore, it exists."

As expected from this discussion of its history, thrombopoietin appears to play an important physiologic role in platelet homeostasis. With the use of a biologic assay, it has been shown that during the course of bone marrow transplantation, thrombopoietin levels are inversely related to the peripheral blood platelet count.[42] Moreover, in a number of other thrombocytopenic disorders (including idiopathic thrombocytopenic purpura), plasma thrombopoietin levels are elevated. The precise inverse relationship between plasma levels of thrombopoietin and the platelet count has led some investigators to propose that platelets regulate the levels of the hormone responsible for their production.[43] Because these data are based on biologic assays of thrombopoietin activity in which platelet-derived inhibitors of thrombopoietic activity could mask the true levels of the hormone, additional studies are required to validate this model. If correct, however, it would appear that thrombopoietin is regulated by some of the same mechanisms proposed for the regulation of macrophage CSF, the cytokine responsible for monocyte and macrophage development.[46]

Thrombopoietin is expressed in many tissues. Northern blot analysis has demonstrated specific messenger RNA in liver, kidney, muscle, and several other tissues.[35,36,47] This widespread distribution seems to be due to its expression in fibroblasts and endothelial cells (unpublished observations),[47] components of the stroma of all organs. Whether its expression is regulated in one or many of these organs, however, is currently under intense study. Congenital deficiency of the hormone may exist; amegakaryocytic thrombocytopenia is a candidate for such a disorder. Whether an acquired state of Tpo deficiency exists, akin to erythropoietin deficiency in renal failure, awaits further study.

Like the clinical successes of erythropoietin and G-CSF, maturation factors for erythrocytes and neutrophils, respectively, thrombopoietin is envisioned to play an important clinical role in states of natural and iatrogenic marrow failure. Toward this end, preclinical trials of the agent have been under way for the past year. Using a combined chemotherapy and radiation protocol that induces profound but nonlethal pancytopenia in mice, we have shown that the daily administration of thrombopoietin

speeds the recovery of platelet counts by nearly two weeks.[48] In a lethal model of pancytopenia, it has been shown that thrombopoietin reduces mortality primarily through a favorable effect on platelet recovery.[49] Studies have been extended to dogs and nonhuman primates. For example, it has been shown that thrombopoietin nearly eliminates radiation-induced thrombocytopenia in baboons.[50] None of these studies have reported any acute or chronic toxic effects. From these studies, it is likely that thrombopoietin will effectively reduce the thrombocytopenic complications of aggressive chemotherapy. Based on these favorable results, clinical trials of the agent are now beginning in patients with cancer. We may be on the verge of a new era of aggressive therapy for cancer.

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Many scientists at ZymoGenetics, Inc, contributed to the work described here by cloning the thrombopoietin complementary DNA. Virginia Broudy, MD, and Thalia Papayannopoulou, MD, provided biologic studies and insights.

REFERENCES

1. Metcalf D: Hematopoietic regulators: Redundancy or subtlety? Blood 1993; 82:3515-3523

2. Ogawa M: Differentiation and proliferation of hematopoietic stem cells. Blood 1993; 81:2844-2853

3. Till JE, McCulloch EA: A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res 1961; 14:213-222

4. Bradley TR, Metcalf D: The growth of mouse bone marrow cells in vitro. Aust J Exp Biol Med Sci 1966; 44:287-299

5. Pluznik DH, Sachs L: The cloning of normal 'mast' cells in tissue culture. J Cell Physiol 1966; 66:319-328

6. Dai CH, Krantz SB, Zsebo KM: Human burst-forming units-erythroid need direct interaction with stem cell factor for further development. Blood 1991; 78:2493-2497

7. Geissler K, Stockenhuber F, Hinterberger W, Balske B, Lechner K: Recombinant human erythropoietin: A multipotential hemopoietic growth factor in vivo and in vitro, *In* Schaefer RM, Heidland A, Horl WH (Eds): Erythropoietin in the Nineties—Contributions to Nephrology, Vol 87. Basel, Karger, 1990, pp 1-10

8. Bot FJ, van Eijk L, Schipper P, Löwenberg B: Effects of human interleukin-3 on granulocytic colony-forming cells in human bone marrow. Blood 1989; 73:1157-1160

9. Metcalf D: Clonal analysis of proliferation and differentiation of paired daughter cells: Action of granulocyte-macrophage colony-stimulating factor on granulocyte-macrophage precursors. Proc Natl Acad Sci USA 1980; 77: 5327-5330

10. Metcalf D, Nicola NA: Proliferative effects of purified granulocyte colony-stimulating factor (G-CSF) on normal mouse hemopoietic cells. J Cell Physiol 1983; 116:198-206

11. Dessypris EN, Krantz SB: Erythropoietin: Regulation of erythropoiesis and clinical use. Adv Pharmacol 1990; 21:127-147

12. Lieschke GJ, Burgess AW: Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor. N Engl J Med 1992; 327: 99-106

13. McDonald TP: Thrombopoietin: Its biology, purification, and characterization. Exp Hematol 1988; 16:201-205

14. Hill RJ, Levin J: Regulators of thrombopoiesis: Their biochemistry and physiology. Blood Cells 1989; 15:141-166

15. McDonald TP, Clift R, Cottrell M: A four-step procedure for the purification of thrombopoietin. Exp Hematol 1989; 17:865-871

16. Hill RJ, Leven RM, Levin FC, Levin J: The effect of partially purified thrombopoietin on guinea pig megakaryocyte ploidy in vitro. Exp Hematol 1989; 17:903-907

17. Tayrien G, Rosenberg RD: Purification and properties of a megakaryocyte stimulatory factor present both in the serum-free conditioned medium of human embryonic kidney cells and in thrombocytopenic plasma. J Biol Chem 1987; 262:3262-3268

18. Erickson-Miller CL, Ji H, Parchment RE, Murphy MJ Jr: Megakaryocyte colony-stimulating factor (Meg-CSF) is a unique cytokine specific for the megakaryocyte lineage. Br J Haematol 1993; 84:197-203

19. Kavnoudias H, Jackson H, Ettlinger K, Bertoncello I, McNiece I, Williams N: Interleukin 3 directly stimulates both megakaryocyte progenitor cells and immature megakaryocytes. Exp Hematol 1992; 20:43-46

20. Avraham H, Vannier E, Cowley S, et al: Effects of the stem cell factor, c-*kit* ligand, on human megakaryocytic cells. Blood 1992; 79:365-371

21. Williams N, Jackson H, Walker F, Oon SH: Multiple levels of regulation of megakaryocytopoiesis. Blood Cells 1989; 15:123-133

22. Ikebuchi K, Wong GG, Clark SC, Ihle JN, Hirai Y, Ogawa M: Interleukin 6 enhancement of interleukin 3-dependent proliferation of multipotential hemopoietic progenitors. Proc Natl Acad Sci USA 1987; 84:9035-9039

23. Paul SR, Bennett F, Calvetti JA, et al: Molecular cloning of a cDNA encoding interleukin 11, a stromal cell-derived lymphopoietic and hematopoietic cytokine. Proc Natl Acad Sci USA 1990; 87:7512-7516

24. Metcalf D, Waring P, Nicola NA: Actions of leukaemia inhibitory factor on megakaryocyte and platelet formation. Ciba Found Symp 1992; 167:174-187

25. Williams N: Is thrombopoietin interleukin 6? Exp Hematol 1991; 19: 714-718

26. Straneva JE, van Besien KW, Derigs G, Hoffman R: Is interleukin 6 the physiological regulator of thrombopoiesis? Exp Hematol 1992; 20:47-50

27. Wendling F, Varlet P, Charon M, Tambourin P: A retrovirus complex inducing an acute myeloproliferative leukemia disorder in mice. Virology 1986; 149:242-246

28. Souyri M, Vigon I, Penciolelli JF, Tambourin P, Wendling F: A putative truncated cytokine receptor gene transduced by the myeloproliferative leukemia virus immortalizes hematopoietic progenitors. Cell 1990; 63:1137-1147

29. Vigon I, Mornon JP, Cocault L, et al: Molecular cloning and characterization of *MPL*, the human homolog of the v-*mpl* oncogene: Identification of a member of the hematopoietic growth factor receptor superfamily. Proc Natl Acad Sci USA 1992; 89:5640-5644

30. Cosman D: The hematopoietin receptor superfamily. Cytokine 1993; 5: 95-106

31. Long MW, Heffner CH, Williams JL, Peters C, Prochownik EV: Regulation of megakaryocyte phenotype in human erythroleukemia cells. J Clin Invest 1990; 85:1072-1084

32. Vigon I, Dreyfus F, Melle J, et al: Expression of the c-*mpl* proto-oncogene in human hematologic malignancies. Blood 1993; 82:877-883

33. Skoda RC, Seldin DC, Chiang MK, Peichel CL, Vogt TF, Leder P: Murine c-*mpl*: A member of the hematopoietic growth factor receptor superfamily that transduces a proliferative signal. EMBO J 1993; 12:2645-2653

34. Methia N, Louache F, Vainchenker W, Wendling F: Oligodeoxynucleotides antisense to the proto-oncogene c-*mpl* specifically inhibit in vitro megakaryocytopoiesis. Blood 1993; 82:1395-1401

35. Lok S, Kaushansky K, Holly RD, et al: Cloning and expression of murine thrombopoietin cDNA and stimulation of platelet production in vivo. Nature 1994; 369:565-568

36. de Sauvage FJ, Hass PE, Spencer SD, et al: Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. Nature 1994; 369:533-538

37. Bartley TD, Bogenberger J, Hunt P, et al: Identification and cloning of a megakaryocyte growth and development factor that is a ligand for the cytokine receptor Mpl. Cell 1994; 77:1117-1124

38. Sohma Y, Akahori H, Seki N, et al: Molecular cloning and chromosomal localization of the human thrombopoietin gene. FEBS Lett 1994; 353:57

39. Kuter DJ, Beeler DL, Rosenberg RD: The purification of megapoietin: A physiological regulator of megakaryocyte growth and platelet production. Proc Natl Acad Sci USA 1994; 91:11104-11108

40. Kaushansky K, Lok S, Holly RD, et al: Promotion of megakaryocyte progenitor expansion and differentiation by the c-*mpl* ligand thrombopoietin. Nature 1994; 369:568-571

41. Wendling F, Maraskovsky E, Debili N, et al: c-Mpl ligand is a humoral regulator of megakaryocytopoiesis. Nature 1994; 369:571-574

42. Nichol J, Hokom MM, Hornkohl A, et al: Megakaryocyte growth and development factor. J Clin Invest 1995; 95:2973-2978

43. Kuter DJ, Rosenberg RD: The reciprocal relationship of thrombopoietin (c-Mpl ligand) to changes in the platelet mass during busulfan-induced thrombocytopenia in the rabbit. Blood 1995; 85:2720-2730

44. Gurney AL, Carver-Moore K, de Sauvage FJ, Moore MW: Thrombocytopenia in c-*mpl*-deficient mice. Science 1994; 265:1445-1448

45. Kaushansky K, Broudy VC, Lin N, et al: Thrombopoietin, the Mpl-ligand, is essential for full megakaryocyte development. Proc Natl Acad Sci USA 1995; 92:3234-3238

46. Bartocci A, Mastrogiannis DS, Migliorati G, Stockert RJ, Wolkoff AW, Stanley ER: Macrophages specifically regulate the concentration of their own growth factor in the circulation. Proc Natl Acad Sci USA 1987; 84:6179-6183

47. McCarty JM, Kaushansky K: Murine Thrombopoietin mRNA Levels Are Modulated by Platelet Count (Abstr). Read at the American Society of Hematology meeting, Nashville, Tennessee, December 1994

48. Sprugel KH, Humes JM, Grossman A, Ren HP, Kaushansky K: Recombinant Thrombopoietin Stimulates Rapid Platelet Recovery in Thrombocytopenic Mice (Abstr). Blood 1994; 84(suppl 1):242A

49. Ulich TR, del Castillo J, Yin S, et al: Megakaryocyte growth and development factor ameliorates carboplatin-induced thrombocytopenia in mice. Blood 1995; 86:971-976

50. Farese AM, Hunt P, Grab LB, Matlick DR, MacVittie TJ: Modulation of Megakaryocytopoiesis in Normal and Sublethally Irradiated Nonhuman Primates By Recombinant Human Megakaryocyte Growth and Development Factor (r-HuMGDF). Presented at the American Society for Blood and Marrow Transplantation annual meeting, Keystone, Colorado, January 1995

Articles

Survey of Illegal Immigrants Seen in an Emergency Department

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There is growing controversy regarding illegal immigrants and their use of social services, including health care, in this country. We surveyed undocumented persons presenting at our emergency department to investigate the reasons why they sought care in the United States. Overall, 227 visits (8.6%) were made in the emergency department by illegal immigrants, mostly Hispanics. Of 104 patients surveyed, all sought care in this country because they were here at the time, and 86 (83%) intended to remain permanently. Of the 104 persons, 83 (80%) cited lack of funding as a reason for seeking emergency department care. Undocumented Hispanics had a higher uninsured rate (64%) than both Hispanics (32%) and non-Hispanics (30%). Of the 104 patients, 38 (36%) had difficulty obtaining care elsewhere because of their status, 53 (51%) knew of no other sources of care, and 46 (44%) said that even if available, only the emergency department was acceptable. Many undocumented persons seek care in the United States because they reside here permanently, often using this emergency department as their source of care. These findings may be important in light of recent efforts to restrict services for this group.

(Chan TC, Krishel SJ, Bramwell KJ, Clark RF: Survey of illegal immigrants seen in an emergency department. West J Med 1996; 164:212-216)

The issue of illegal immigrants residing in the United States has generated tremendous controversy. Defined as persons who have entered the United States illegally or violated the terms of their residency status, illegal immigrants number anywhere from 2 to 8 million. Most originate from Mexico or Central America and reside in the Southwest, particularly California.[1-5]

There is a growing perception that these persons place an undue burden on public-supported social services in this country.[6,7] Many believe that some Mexican citizens cross the border specifically to obtain medical services in the United States.[7-9] The media have focused public attention on the high cost of providing health care to illegal immigrants, and there is mounting public sentiment to restrict access to services for this population (G. Cowley, A. Murr, "Good Politics, Bad Medicine," *Newsweek*, December 5, 1995, pp 32-34). California's recently passed Proposition 187, which restricts nonemergency medical care for undocumented noncitizens living in the state, reflects this sentiment.[10] Moreover, the issue of illegal immigrants has become increasingly important in discussions regarding current health care policy.[11,12]

Previous research indicates that undocumented persons obtain health care in the United States primarily through hospital emergency departments.[1-3,13-18] To examine this issue further, we surveyed a sample of illegal immigrants seen at a university hospital emergency department to determine their reasons for seeking medical care in this country.

Patients and Methods

This study was conducted at a university hospital emergency department located 32 km (20 mi) from the United States-Mexico international border. Registration personnel routinely ask all patients to state their ethnicity and current residency status on arrival and to provide some proof of identification. This information is obtained for statistical purposes only. Patients who stated they were either undocumented or a foreign citizen (but not a tourist, visa recipient, or legal resident of this country) were identified as illegal immigrants by retrospective review of data collected during a one-month time period, from February 1 through 28, 1994. The emergency department medical records of these patients were reviewed to determine demographic data, insurance status, use of prehospital care, and acuity and disposition from the emergency department. Data were compared with those of all other patients during the same time period. Statistical analysis of the data was conducted by the χ^2 test to compare categorical variables. A P value of less than .05 was considered statistically significant.

We conducted a telephone survey of all undocumented persons identified in the manner described. A bilingual research assistant did the surveys during the one- to

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four-month period following the patient's emergency department visit. Informed consent was obtained from all participants. For pediatric patients, the parents or legal guardians were surveyed. Patients were asked the following questions: place of origin, country of primary residence, length of residence, and anticipated length of stay in the United States; reasons for seeking care at the university hospital emergency department in this country; knowledge and acceptance of alternative sources of care; and difficulty with access to care in the past.

Results

There were 2,721 patient visits to the emergency department during the month of February 1994. Of these, 2,629 patients (96.6%) had sufficient citizenship and ethnicity data recorded for study purposes. A total of 227 (8.6%) visits were made by patients identified as illegal immigrants (Table 1). Of these, 203 (89.4%) were made by persons of Hispanic ethnicity (Table 2). Hispanics accounted for 841 of all emergency department visits, 24.1% of which were attributable to illegal immigrants (Table 3).

Table 4 shows the age distribution of patients seen in the emergency department. Most undocumented Hispanic patients were in the 10- through 29-year age range. Of note, 36.9% of Hispanic patients with legal residence were younger than 10 years.

About a third of emergency department visits (33.6%) were made by unfunded patients who had no insurance (Table 5). Undocumented Hispanics had a significantly higher rate of unfunded visits than both Hispanic and non-Hispanic legal residents (64.5% versus 32.1% and 30.4%, respectively; $P < .001$; Table 5).

Both undocumented Hispanics and Hispanics with legal residence were significantly less likely than non-Hispanic legal residents to access the prehospital care system and arrive by ambulance (10.3% and 9.0%, respectively, versus 18.3%; $P < .05$; Table 5). Table 6 reflects the acuity of illness or the triage score as determined by the triage nurse on patients' arrival to the emergency department.

The admission rate for undocumented Hispanics was slightly higher than the rate for all emergency department patients (20.2% versus 17.6%, $P > .05$ [not significant]). A similar trend was found when undocumented Hispanics were compared with Hispanics who were legal residents (20.2% versus 15.7%, $P > .05$; Table 5).

TABLE 1.—*Residency Status of Patients Seen in the Emergency Department February 1 through 28, 1994*

Status	Patients No.	Patients (%)
Total registered patient visits studied	2,629	(100.0)
Legal residents or citizens	2,383	(90.6)
Tourist or visa*	10	(0.4)
Amnesty†	9	(0.3)
Undocumented	227	(8.6)

*Patients who claimed to be foreign citizen tourists or on visas in the United States.
†Patients who claimed they were granted amnesty under current federal law.

TABLE 2.—*Undocumented Patients by Race and Ethnicity*

Race or Ethnicity	Patients No.	Patients (%)
Total	227	(100.0)
Hispanic	203	(89.4)
Asian or Pacific Islander	13	(5.7)
Black	7	(3.1)
White	4	(1.8)

TABLE 3.—*Hispanic Patient Emergency Department Visits by Residency Status*

Residency Status	Patients No.	Patients (%)
Total patient visits	841	(100.0)
Legal residents or citizens	632	(75.1)
Undocumented	203	(24.1)
Tourist or visa	3	(0.4)
Amnesty	3	(0.4)

Survey Data on Undocumented Hispanic Patients

Overall, 174 undocumented Hispanic patients sought care at the emergency department during the study period (for a total of 203 visits, of which 29 were repeat visits by certain persons). We contacted 104 (60%) of these patients, all of whom consented to the survey. Of the 104 patients, 96 (92%) were from Mexico, and 3 were from Central America. The average length of time living in the United States was 7.9 years, with a median of 6 years.

All 104 respondents sought care in the United States instead of Mexico (or other country of origin) because they were in this country at the time care was needed. At the time of our survey, 99 (95%) were still residing in the United States, and 5 (5%) were residing in Mexico. A total of 90 (86%) said that their primary residence was in the United States, and 86 (83%) planned on remaining here permanently.

When asked to cite reasons for seeking care at the university hospital emergency department, 63 (61%) cited the lack of health insurance coverage. An additional 20 respondents (19%) said that their restricted Medi-Cal benefits required them to seek medical care at an emergency department for coverage (Medi-Cal currently provides coverage for noncitizens that is restricted to prenatal and emergency care only[9,19,20]). Other reasons included previous care at the hospital (61%), the need for specialized care (57%), the perception that they would receive better care (39%), and the recommendations of others (41%). A total of 38 respondents (36%) had difficulty obtaining care from other outpatient

TABLE 4.—*Age of Patients Seen at the University Hospital Emergency Department (n = 2,610) by Residency Status and Ethnicity, No. (%)**

Residency Status and Ethnicity	Tatal	Age, years 0-9	10-19	20-29	30-39	40-49	50-59	≥60
Non-Hispanic legal residents.....	1,751	196 (11.2)	102 (5.8)	331 (18.9)	447 (25.5)	326 (18.6)	166 (9.5)	183 (10.5)
Non-Hispanic undocumented....	24	1 (4.2)	3 (12.5)	5 (20.8)	5 (20.8)	2 (8.3)	3 (12.5)	5 (20.8)
Hispanic legal residents.....	632	233 (36.9)	65 (10.3)	92 (14.6)	110 (17.4)	67 (10.6)	29 (4.6)	36 (5.7)
Hispanic undocumented....	203	19 (9.4)	35 (17.2)	83 (40.9)	34 (16.7)	13 (6.4)	8 (3.9)	11 (5.4)

*Data for patients classified under "Amnesty," "Visa," or "Tourist" not included (n = 19).

sources, including other clinics and hospitals, because of their undocumented status.

Of the 104 patients, 53 (51%) knew of no alternative sources of care. Of those who did know, only 23 (22%) sought care there before presenting at our emergency department: 22 at outpatient clinics in the United States, and 1 in Mexico. Of the respondents, 58 (56%) were willing to seek care at alternative sources if available in the United States, whereas only 11 (11%) were willing to do so in Mexico. Nearly half (44%) said that no source, in or outside the United States, would be an acceptable alternative to the emergency department.

Discussion

Research on illegal immigrants and their use of health care has been problematic. They are often migratory, fearful of detection, and have proved difficult to contact and trace over time.[3,14] Past studies used different techniques to survey this population. These methods have included random household telephone surveys on both sides of the border[7,19,20] and direct personal surveys in the field by means of a "snowball" technique whereby researchers were referred to others by those already surveyed.[14] Although partially successful at reaching this population, most reports on illegal immigrants have relied on generalizations and assumptions.[2,3,9,13]

Current estimates of the undocumented population in San Diego County range from 50,000 to 200,000, or about 9% of the entire county population.[3] According to the 1990 census, Hispanics with legal residence account for 20% of the county population and have a lower median income and a higher percentage of families living below the poverty level. A large segment of this population is born outside the United States.[21]

Unlike past studies, we surveyed undocumented patients of Hispanic or Latino ethnicity who admitted their status on registering for emergency department care. Because proof of identification is requested but not required, our method missed persons who misrepresented their true status and may have underestimated the actual number of undocumented patients. Nearly 9% of all visits, however, were made by undocumented persons, which correlates closely with government estimates that 9.3% of all emergency department visits in our county are attributable to this population.[3]

We were able to survey about 60% of these undocumented persons. Remarkably, every person contacted readily agreed to participate in our study after reassurances that identifying information would be kept confidential. Those who were not contacted had given either an incorrect or no telephone number at registration. Undocumented persons who provided no legitimate means of contacting them may have feared the consequences if such information were known. Others may be homeless, migratory, or simply lack access to a telephone or other means by which they could be contacted.

Differences may exist between the population of illegal immigrants who provided correct telephone numbers and those who did not. Previous studies have established that the undocumented population consists of two groups: "settlers," those who permanently reside in the United States and have established social connections in this country; and "sojourners," who are more migratory, residing on a temporary basis in both countries.[1,11-13,22] Most persons surveyed had been living in the United States for several years and planned on staying permanently. As a result, our survey may be skewed toward those undocumented immigrants permanently settled in this country.

Many of those surveyed used the emergency department as their primary source of care, as reflected by our high rate of repeat visits. A large number were simply unaware of any other sources of care, with more than 40% stating that no alternative to the emergency department was acceptable. This finding may reflect the socioeconomic condition of this population, as most persons surveyed had no health coverage. Lack of knowledge of how to appropriately access care and language and other cultural factors may also play important roles as barriers to health care.[2,4,23-27]

More than a third of our respondents said they had difficulty accessing care at other sites because of their undocumented status. Previous studies suggest the important role the fear of detection and deportation has in discouraging undocumented persons from obtaining care.[2,4,13,26,28] In certain localities, legal restrictions limit

TABLE 5.—*Admission, Insurance, and Rates of Prehospital Care Ambulance Use for Emergency Department (ED) Patient Visits by Residency Status and Ethnicity, No. (%)*

Residency Status and Ethnicity	*Total*	*Admission*	*No Funding*	*Ambulance Use*
All ED patient visits	2,629*	462 (17.6)	883 (33.6)	403 (15.3)
Non-Hispanic legal residents	1,751	315 (18.0)	533 (30.4)	320 (18.3)
Non-Hispanic undocumented	24	4 (16.7)	6 (25.0)	4 (16.7)
Hispanic legal residents	632	99 (15.7)	203 (32.1)	57 (9.0)
Hispanic undocumented	203	41 (20.2)	131 (64.5)	21 (10.3)

*Data for patients classified under "Amnesty," "Visa," or "Tourist" not included (n = 19).

TABLE 6.—*Arrival Triage Acuity Scores for Patients Seen at the University Hospital Emergency Department by Residency Status and Ethnicity, No. (%)*

	*Triage Acuity Score**				
Residency Status and Ethnicity	*Total*	*Level 1*	*Level 2*	*Level 3*	*Level 4*
Non-Hispanic legal residents	1,751	155 (8.8)	808 (46.1)	765 (43.7)	23 (1.3)
Non-Hispanic undocumented	24	4 (16.7)	11 (45.8)	9 (37.5)	0 (0.0)
Hispanic legal residents	632	33 (5.2)	317 (50.2)	278 (44.0)	4 (0.6)
Hispanic undocumented	203	10 (4.9)	98 (48.3)	91 (44.8)	4 (2.0)

*Triage score levels: 1 = immediate: acute illness requiring immediate medical attention with loss of life or function imminent; 2 = emergent: illness requiring attention within 1 hour; 3 = delayed: minor complaints that can by treated in the same day; 4 = nonemergent: minor complaints of chronic nature.

their use of medical services, and providers may attempt to screen for citizenship status.[4]

Our findings have important implications for health care policies directed at undocumented noncitizens. Currently, efforts such as Proposition 187 are underway to deny nonemergency health care for undocumented immigrants as a measure of containing costs.[6,10] Whereas the cost issue remains the central factor driving the public debate on undocumented persons, other concerns must be addressed when considering such policies.

Our study suggests that many illegal immigrants live in this country on a permanent basis and are unwilling to obtain care outside the United States. This population already uses the emergency department as its main and often sole source of care. Further limiting access of these persons to routine medical services may simply result in shifting more of their care to emergency departments in this country. In addition, the expected cost savings of laws such as Proposition 187 may be lower than anticipated. Denying regular care to undocumented noncitizens may discourage them from seeking medical attention in a timely manner. Such persons may then present to an emergency department with more acute medical conditions that require more costly treatment.

Even if these policies did encourage some undocumented persons who are more migratory to seek care outside the United States, the ramifications of such laws on the health care of undocumented immigrants permanently settled in this country raise serious ethical and public health concerns. For example, our survey found that most undocumented Hispanics seen in our emergency department were young adults, whereas a large percentage of those with legal residence were young children. This large pediatric population may be a result of children born to undocumented persons in this country. Under policies such as Proposition 187, health care will be available for these children who are US citizens by birth, but denied to their parents living in this country.

In addition, new immigrants and undocumented persons often live in environmental conditions that promote the spread of infectious and communicable diseases such as tuberculosis. This population represents a substantial public health threat to society as a whole if regular care and treatment are not available.[6,9,28-30]

Goals such as cost containment and universal coverage may never be met unless the undocumented population has been considered. A greater understanding of how these persons access health care and their reasons for doing so in the United States must be explored to address relevant health policy issues. In addition, future studies should examine and focus on specific policies and programs that affect the health and medical care of illegal immigrants living in this country.

Conclusion

A substantial number of illegal immigrants are permanent residents in the United States and have lived here for many years. They seek medical care here because they live in this country, consider the United States their primary residence, and are unwilling to obtain health care outside the United States. For a variety of reasons, many undocumented persons use emergency departments as their main and often only source of health care, including primary and nonemergency care. Policies such as Proposition 187 aimed at decreasing health care expenditures by denying routine and nonemergency medical care to the undocumented population may not be successful. Policy makers must consider the illegal immigrant population when addressing relevant health policy issues.

REFERENCES

1. Cornelius WA, Chavez LR, Castro JG: Mexican Immigrants and Southern California: A Summary of Current Knowledge—Research Report Series 36 for the Center for United States-Mexican Studies, University of California, San Diego, 1982

2. Health Needs Along the United States-Mexico Borderlands—Report to the US House of Representatives. US Public Health Service, National Center for Health Services Research and Health Care Technology Assessment, 1986-1987

3. Fiscal Impact Analysis of Undocumented Immigrants Residing in San Diego County. Sacramento, Office of the Auditor General, State of California, August 1992, C-126

4. Loue S: Access to health care and the undocumented alien. J Legal Med 1992; 13:271-332

5. Siddharthan K, Alalasundaram S: Undocumented aliens and uncompensated care: Whose responsibility? Am J Public Health 1993; 83:410-412

6. Ziv TA, Lo B: Denial of care to illegal immigrants—Proposition 187 in California. N Engl J Med 1995; 332:1095-1097

7. Guendelman S, Jasis M: Measuring Tijuana residents' choice of Mexican or United States health care services. Public Health Rep 1990; 105:575-583

8. Guendelman S: Health care users residing on the Mexican border: What factors determine choice of the United States or Mexican health system? Med Care 1991; 29:419-429

9. Morain C: Lot of guesswork, little data, on Proposition 187's effects. Am Med News 1995 Feb 20; 38:4-5

10. Office of the Secretary of State, State of California: 'Illegal Aliens—Ineligibility for Public Services. Verification and Reporting. Initiative Statute.' [filed January 10, 1994; ballot approved June 23, 1994; passed November 8, 1994]

11. Pallarito K, Wagner L: Administration's plans for care of illegal aliens questioned. Mod Healthcare 1993 Oct 18; 23:12

12. Pallarito K, Kertesz L, Lutz S, Greene J: Bridging the gap: Health care reform and illegal aliens. Mod Healthcare 1994 Jul 4; 24:24-32

13. Community Research Associates, Inc: Undocumented Immigrants: Their Impact on the County of San Diego—Report prepared for the County of San Diego, May 1980

14. Chavez LR, Cornelius WA, Jones OW: Mexican immigrants and the utilization of US health services: The case of San Diego. Soc Sci Med 1985; 21: 93-102

15. Andersen RM, Giachello AL, Aday LA: Access of Hispanics to health care and cuts in services: A state-of-the-art overview. Public Health Rep 1986; 101:238-252

16. Muñoz E: Care for the Hispanic poor: A growing segment of American society. JAMA 1988; 260:2711-2712

17. Poma PA: The Hispanic health challenge. J Natl Med Assoc 1988; 80:1275-1277

18. White-Means SI, Thornton MC, Yeo JS: Sociodemographic and health factors influencing black and Hispanic use of the hospital emergency room. J Natl Med Assoc 1989; 81:72-80

19. Hubbell FA, Waitzkin H, Mishra SI, Dombrink J, Chavez LR: Access to medical care for documented and undocumented Latinos in a southern California county. West J Med 1991; 154:414-417

20. Guendelman S, Jasis M: Giving birth across the border: The San Diego-Tijuana connection. Soc Sci Med 1992; 34:419-425

21. 1990 Census of the United States—Census of Population and Housing, Characteristics for Census Tracts and Block Numbered Areas, San Diego, California. US Dept of Commerce, 1990

22. Chavez LR: Settlers and sojourners: The case of Mexicans in the United States. Hum Organ 1988; 47:95-108

23. Council on Scientific Affairs: Hispanic health in the United States. JAMA 1991; 265:248-252

24. Woloshin S, Bickell NA, Schwartz LM, Gany F, Welch G: Language barriers in medicine in the United States. JAMA 1995; 273:724-728

25. Moore P, Hepworth JT: Use of perinatal and infant health services by Mexican-American medicaid enrollees. JAMA 1994; 272:297-304

26. Walker G: Utilization of health care: The Laredo migrant experience. Am J Public Health 1979; 69:667-672

27. Bergner L, Yerby AS: Low income and barriers to use of health services. N Engl J Med 1968; 278:541-546

28. Asch S, Leake B, Gelberg L: Does fear of immigration authorities deter tuberculosis patients from seeking care? West J Med 1994; 161:373-376

29. McKenna MT, McCray E, Onorato L: The epidemiology of tuberculosis among foreign-born persons in the United States: 1986-1993. N Engl J Med 1995; 332:1071-1076

30. Nickel JW: Should undocumented aliens be entitled to health care? Hastings Center Rep 1986; 16:19-23

Articles

Effect of Changes in the Health Care System on the Career Outlook of University of Washington, Seattle, Medical Students

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We describe how market-oriented and governmental reforms were shaping students' career choice and outlook toward future clinical practice during the 1993-1994 academic year. A random sample of a third of University of Washington, Seattle, medical students (n = 212) was surveyed regarding attitudes toward health care reform, specialty choice, and future clinical practice; 171 responded (81%). Most students (90%) thought that the health care system required fundamental change. An equal proportion favored managed competition and single-payer proposals (40% and 39%, respectively). Most (72%) were confident that they would be able to practice medicine in a professionally satisfying environment. More than half the students interested in specialty careers thought that they might not be able to practice in their chosen field, but only 21% of these were more likely to choose a career in primary care in light of anticipated reforms. Most students were optimistic about their future medical careers. Knowledge of market-oriented reforms exerted little influence on the career decisions of students interested in nonprimary care fields. Medical schools should play a more active role at the undergraduate level so that those students who apply to medical school have a better understanding of the changing nature of health care delivery in this country.

(Piehl JH, Lessler DS, Schaad D: Effect of changes in the health care system on the career outlook of University of Washington, Seattle, medical students. West J Med 1996; 164:217-221)

Ongoing changes in our health care system will likely influence the future career satisfaction of today's medical students. The effects of these changes on medical students' attitudes toward a medical career have not been well described, however.

Recent surveys suggest that many practicing physicians are dissatisfied with their medical careers. For example, 37% of American physicians would advise a qualified college student against pursuing a career in medicine,[1] and among physicians younger than 40 years who had been in practice more than one but fewer than seven years, only 60% would still go to medical school.[2] The relative dissatisfaction of physicians with medical practice may relate to the rapidly changing practice environment.[2] In particular, physicians increasingly practice as part of integrated managed care networks (for example, health maintenance organizations) that constrain autonomy and impose administrative burdens.[3]

Unlike many of today's physicians who chose their fields and entered practice before the rapid growth of managed care and government regulation, today's students have the opportunity to consider the corporatization of health care and possible governmental reforms in making their career decisions. If they are well informed about the complex health care environment in which they will practice, they may experience less discordance than their predecessors between the expectations and realities of clinical practice. As a result, today's students may be more satisfied with their medical careers.

An understanding of the changing physician resource needs of our health care system could also possibly affect students' choice of specialty. In fact, some experts have suggested that market forces may make a regulatory approach to redressing the imbalance of generalist-to-specialist physicians unnecessary.[4] Therefore, we undertook a survey to assess the attitudes of University of Washington medical students toward their future medical careers and the degree to which they feel that health care reform will affect their career choices.

Method

We surveyed a random sample of a third of each of the four medical school classes at the University of Washington School of Medicine during the 1993-1994 academic year. Students who had withdrawn or were on leaves of absence were excluded before the sampling.

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ABBREVIATIONS USED IN TEXT

MCAT = Medical College Admission Test
MS III, IV = third- and fourth-year medical students

TABLE 1.—*Comparison of Medical Students' and Physicians' Views of the US Health Care System**

Respondents	Changes Needed in Health Care System: Minor, %	Fundamental, %	Rebuild, %	Don't Know, %
Medical students	9	81	10	0
Physicians	51	39	7	3

*From Blendon et al.[3]

The survey instrument included 20 items covering demographic information, views on the American health care system, and attitudes toward health care changes and career choices. One question, "Which of the following statements most closely expresses your view of the current American health care system?" had been posed in several physician surveys[5-7] and was included to allow comparison of the medical students with physicians. All questions regarding attitude toward future medical career were scored on a five-point Likert scale from disagree strongly (1) to agree strongly (5). (A copy of the questionnaire is available on request.) The questionnaires were mailed in February 1994 with a second mailing three weeks after the first. All responses were received by April 1, 1994.

Responders and nonresponders were compared using demographics, grade-point averages, and test scores. Demographic information was obtained from the University of Washington School of Medicine Biographical and Career Preference Inventory, a questionnaire completed by each student on the first day of matriculation with a compliance rate of approximately 98%. Grade-point averages and Medical College Admission Test (MCAT) scores for each student were provided to the school by the American Medical College Admission Service, with National Board of Medical Examiners Step One scores provided by the National Board of Medical Examiners.

For the purposes of this survey, primary care was defined as family medicine, general internal medicine, and general pediatrics. Nonprimary care was defined as all other specialties, excluding research and academic medicine. Clinical students were defined as third-year (MS III) and fourth-year (MS IV) students, with preclinical referring to first-year (MS I) and second-year (MS II) students.

Analysis

For our analysis, we used StatPac Gold software (copyright 1988 and 1992 by Walonick Associates, Incorporated). In addition to descriptive statistics, we used χ^2 analysis or the Fisher's exact test to compare responses for nominal variables between subgroups of students and Student's t test for continuous variables. Statistical significance was defined as a P value of less than .05.

Results

Of 220 students surveyed, 175 responded. Eight responses were excluded from the analysis: two from students who were pursuing research as part of the MD-PhD degree program, two because of a clerical error in their distribution, and four because they were undeliverable. The adjusted response rate was 81%.

Responses were evenly distributed among all four classes. An analysis of responders versus nonresponders yielded no significant difference between age, sex, undergraduate grade-point average, and undergraduate hours. Among those students who took the MCAT before changes in 1991 (MS IIIs and MS IVs), the only significant difference was that responders scored a mean reading score of 9.7 versus a nonresponder mean of 8.7 ($P <$ .01). There were no differences in MCAT subscores for those taking the test after 1991.

Most students (80%) thought that there were some good things in the American health care system, but that fundamental changes were needed to make it work better. About equal numbers thought that the system needed only minor changes (9%) or that it had to be completely rebuilt (10%) (Table 1).

An equal number of students (40%) favored managed competition, defined as a combination of market forces and government regulations to encourage competition among private health plans, with access provided through an employer mandate, or single-payer proposals (39%), defined as everyone receiving coverage from a

TABLE 2.—*Medical Students' Views of Health Care Reform Proposals*

Question	Proposed Health Care Reform: No Change, %	Managed Competition, %	Single Payer, %	Incremental Change, %	Government Vouchers, %
Which of the following changes in the American health care system do you most *favor*?	1	40	39	8	12
Which of the following changes in the American health care system do you most *expect*?	6	58	6	24	6

TABLE 3.—*Medical Students' Outlook Toward the Future*

Statement	*Strangly Agree, %*	*Agree, %*	*Neutral, %*	*Disagree, %*	*Strongly Disagree, %*
Given what I know about how medicine is likely to be practiced in the future,					
if I were making the decision today, I would still decide to go to medical school	59	28	9	3	1
I am confident that I will be able to practice medicine in a professionally satisfying environment	27	45	15	11	2
As a result of changes in the health care system,					
I am more likely to practice as a salaried employee of a large group/multispecialty practice or HMO	7	44	24	19	6

HMO = health maintenance organization

public plan, with care provided through the private sector, with 8% favoring incremental change (Table 2). When asked which change in the American system they most expected, 58% of students responded managed competition, 24% incremental change, and 6% a single-payer system. About half (52%) thought that implementation of the proposal that they most favored would take between five and nine years, with 26% expecting three to four years, and 15% anticipating ten or more years.

A total of 87% of all students would still decide to go to medical school, and 72% were confident that they would be able to practice medicine in a professionally satisfying environment. About half (51%) of students anticipated practicing as a salaried employee of a large organization (Table 3).

Of all respondents, 51% planned a career in primary care, 30% in nonprimary care, and 18% were undecided. Of the students planning to enter a nonprimary care field, 58% agreed with the statement that they might not be able to practice in the specialty of their choice as a result of changes in the health care system, versus 11% of students planning a career in primary care ($P < .001$). Students planning to enter nonprimary care fields, however, were less likely than those planning careers in primary care to agree with the statement that "As a result of changes in the health care system, I am more likely to choose a career in family practice/general internal medicine/general pediatrics" (21% and 39%, respectively; $P < .03$) (Table 4).

Although there were no significant differences in sex or between clinical and nonclinical students with respect to attitudes toward health reform proposals or perspectives on the future, 62% of female students planned to specialize in primary care versus 44% of male students ($P < .03$).

Discussion

Changes in the organization and financing of health care delivery over the past decade have engendered broad-based discontent among practicing physicians.[1-3] The current dissatisfaction with medicine is often linked to the increasing domination of the health care system by managed care plans. These market-oriented changes and proposed governmental reforms have implications for the careers of today's medical students. Whereas several surveys have assessed the attitudes of practicing physicians toward health care reform, few studies have examined medical students' attitudes toward reform,[8,9] and none to our knowledge have looked at the effects of reforms on students' attitudes toward their future medical careers.

At the time of our survey, the vast majority of University of Washington students thought that fundamental reform was necessary, but students were evenly split in their support of a single-payer system and managed competition. The students' views about the current system differed markedly from those of practicing physicians. In particular, 90% of students thought that the health care system needed either fundamental change or to be rebuilt completely, compared with 46% of practicing physicians (see Table 1).[5] Practicing physicians were also much less likely than students to favor a single-payer system (19% versus 38%, respectively).[5]

As the subjects for this study come from only one medical school, care must be taken in generalizing the results to the nation as a whole. The University of Washington School of Medicine has a demographic profile substantially different from the national average. Washington students are older—55% are between the ages of 25 and 29, with 31% between 20 and 24 versus 20% and 75%, respectively, nationwide—have equal gender representation compared with 57% male nationwide, and have a higher percentage of European Americans than the national average for medical schools.[10] Thus, a national sample would need to be done before we could draw any broad national conclusions about medical students' attitudes toward health reform. Furthermore, the contrasting opinions of Washington medical students and US physicians might have, in part, reflected the progressive politics of Washington State at the time this survey was performed. At that time, the state was implementing a reform package similar to President Clinton's failed Health Security Act,[11] and one

TABLE 4.—*Medical Students' Views of Current Career Choice*

Statement	*Strongly Agree, %*	*Agree, %*	*Neutral, %*	*Disagree, %*	*Strongly Disagree, %*
*As a result of changes in the health care system, I may not be able to practice in the specialty that most interests me**					
Students planning a career in primary care	0	11	18	33	38
Students planning a career in nonprimary care	9	49	6	24	12
As a result of changes in the health care system, I am more likely to choose a career in family practice/general internal medicine/general pediatrics†					
Students planning a career in primary care	9	30	33	20	8
Students planning a career in nonprimary care	0	21	18	43	18

*$P<.001$.
†$P<.03$.

Washington Representative, James McDermott, MD, had taken the lead in Congress to advance a single-payer system for the nation.[12] Because of these influences on the health care debate in Washington State, University of Washington students might have been more likely to believe in the need for fundamental reform than others in this country.

Despite the uncertainty surrounding future government and market-oriented reforms at the time, the students surveyed remained optimistic about their future careers—most thought that they would be able to practice in a professionally satisfying environment, and virtually all would have still decided to go to medical school if they had had to make that decision at the time of the survey. The students also expected changes in the organization and the delivery of health care: half the respondents thought that as a result of changes in the health care system, they would be more likely to practice as a salaried employee of a large group or multispecialty practice or health maintenance organization.

Whether students will experience less dissatisfaction with their future careers than those physicians already in practice remains unclear. On the one hand, that half of the students surveyed thought it likely that they would practice in a large organization suggests that these students may be more accepting of the constraints on clinical practice and other administrative burdens inherent in practicing in such a setting, especially compared with their counterparts who entered practice during a different era. On the other hand, the substantial number of students who planned to pursue a nonprimary care field despite acknowledging that they might not be able to practice in the specialty of their choice raises concern that these future physicians may experience dissatisfaction with their careers.

Our finding that students who were planning to pursue a specialty career lacked confidence that they would be able to practice in their chosen fields despite being overwhelmingly content with their choice of medicine as a career and optimistic about their futures is perhaps the most intriguing aspect of this study. The University of Washington is a premier institution for training in primary care. As a result of an admissions policy that screens for an interest in primary care, a preclinical curriculum that includes a required course devoted to health policy, and strong mentorship from primary care physicians, University of Washington students are far more likely to enter primary care residencies: 50% versus 29% for the nation as a whole in 1994.[13] Our data indicate that, in 1994, market-oriented reforms were exerting little additional influence on the career choices of students interested in specialty careers. Indeed, only 21% of respondents planning to enter a nonprimary care field said that, as a result of changes in the health care system, they were more likely to choose a career in primary care. This translates into a possible career shift toward primary care for only 11 respondents out of 50 possible candidates.

We can only speculate as to why students interested in nonprimary care careers were embarking on such careers, even though the majority agreed that as a result of changes in the health care system, they might not be able to practice in their specialty of choice. Perhaps the desire of these students to practice in a specialty was so great that they were willing to live with the uncertainty of whether or not it would be possible for them to find work in their chosen field after completing a relatively lengthy and arduous training period. Alternatively, nonprimary care students might have been, at some level, denying the reality they had so readily acknowledged in our survey. In fact, the dean's office at the University of Washington, in counseling students that urban opportunities to practice may be limited in the future, has seen students who feel that whereas other students might have difficulty practicing their chosen career, this will not be

the case for them (Carol MacLaren, PhD, Assistant Dean for Student Affairs, University of Washington School of Medicine, oral communication, June 1994).

Although Washington State and the nation have dramatically scaled back governmental reforms of the health care system since this survey was done, market-driven reform has continued at a rapid pace. One study estimates that, as a result of market-driven changes in health care in the United States, there will be an excess of about 165,000 specialists by the year 2000.[14] Thus, it is disturbing that in our survey the majority of students who planned to pursue nonprimary care specialties were unaffected by the economic, political, and academic forces encouraging them to enter primary care. This finding underscores the need for medical schools to educate students about the ongoing and rapid changes in health care in our society. Moreover, we think that medical schools should institute formal career counseling programs during the preclinical years and play a more active role at the undergraduate level so that those students who choose to apply to medical school do so with a better understanding of the changing nature of health care delivery in this country.

REFERENCES

1. Blendon RJ, Donelan K, Leitman R, et al: Physicians' perspectives on caring for patients in the United States, Canada, and West Germany. N Engl J Med 1993; 328:1011-1016

2. Cohen AB, Cantor JC, Barker DC, Hughes RG: Young physicians and the future of the medical profession. Health Aff (Millwood) 1990; 9:138-148

3. Lewis CE, Prout DM, Chalmers EP, Leake B: How satisfying is the practice of internal medicine? A national survey. Ann Intern Med 1991; 114:1-5

4. Iglehart JK: Health policy report: Health care reform and graduate medical education. N Engl J Med 1994; 330:1167-1171

5. Blendon RJ, Kohut A, Benson JM, Donelan K, Bowman C: Health system reform—Physicians' views on the critical choices. JAMA 1994; 272:1546-1550

6. Byrd WM, Clayton LA, Kinchen K, et al: African-American physicians' views on health reform: Results of a survey. J Natl Med Assoc 1994; 86:191-199

7. Malter AD, Emerson LL, Krieger JW: Attitudes of Washington State physicians toward health care reform. West J Med 1994; 161:29-33

8. Wilkes MS, Skootsky SA, Hodgson CS, Slavin S, Wilkerson L: Health care reform as perceived by first year medical students. J Community Health 1994; 19:253-269

9. Schnipper J, Dorwart RA: Medical students' opinions of health system reform. JAMA 1995; 273:80-81

10. Section for Educational Research: 1992 Matriculating Student Survey Results—All Schools Summary. Washington, DC, Association of American Medical Colleges, 1993

11. Crittenden RA: Managed competition and premium caps in Washington State. Health Aff (Millwood) 1993; 12:82-88

12. McDermott J: Evaluating health system reform—The case for a single-payer approach. JAMA 1994; 271:270-284

13. National Resident Matching Program: NRMP Data Booklet. Washington, DC, NRMP, March 1994

14. Weiner JP: Forecasting the effects of health reform on US physician workforce requirement: Evidence from HMO staffing patterns. JAMA 1994; 272:222-230

Articles

High-Altitude Pulmonary Edema at a Ski Resort

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Medical records of 150 patients with high-altitude pulmonary edema seen over a 39-month period in a Colorado Rocky Mountain ski area at 2,928 m (9,600 ft) (mean age, 34.4 years; 84% male) were reviewed. The mean time to the onset of symptoms was 3 ± 1.3 days after arrival. Common symptoms were dyspnea, cough, headache, chest congestion, nausea, fever, and weakness. Orthopnea, hemoptysis, and vomiting were rare, occurring in 7%, 6%, and 16%, respectively. Symptoms of cerebral edema occurred in 14%. A temperature exceeding 100°F occurred in 20%, and 17% had a systolic blood pressure of 150 mm of mercury or higher. Blood pressures were higher in patients older than 50 years (142 mm of mercury). Rales were present in 85%, and a pulmonary infiltrate was present in 88%; both were most commonly bilateral or on the right side. The amount of infiltrate was mild. Men appeared to be more susceptible than women to high-altitude pulmonary edema. Pulse oximetry in 45 patients showed a mean oxygen saturation of 74% (38% to 93%). Treatment methods depended on severity and included a return to quarters for portable nasal oxygen, an overnight stay in the clinic for continuing oxygen, or a descent to Denver for recovery or admission to a hospital. All patients received oxygen for 2 to 4 hours in the clinic. There were no deaths or complications.

(Hultgren HN, Honigman B, Theis K, Nicholas D: High-altitude pulmonary edema at a ski resort. West J Med 1996; 164:222-227)

Many persons visit high-altitude areas above 2,624 m (8,000 ft) to participate in recreational activities, attend seminars and concerts, and for business reasons. The Colorado Board of Tourism has estimated that more than 13 million persons visited the Colorado mountains in 1990. It has been shown that about 25% of these high-altitude visitors will experience some discomfort due to acute mountain sickness, and about 14% will have symptoms severe enough to limit normal activity for 24 hours.[1] Although the incidence of high-altitude pulmonary edema (HAPE) in such visitors is low, the large population involved results in many cases of HAPE being seen by physicians, especially during the ski season. Whereas fatalities are rare, an episode of pulmonary edema is unpleasant and may interrupt a long-planned holiday. It is important for physicians and ancillary medical personnel to be acquainted with the clinical features of HAPE so that a prompt diagnosis can be made and appropriate treatment carried out. There is little information concerning HAPE in visitors to Rocky Mountain resorts.[2,3] For this reason, we examined the clinical features of 150 patients with HAPE seen at a ski resort in Summit County, Colorado, altitude 2,928 m (9,600 ft), over a 39-month period.

Patients and Methods

We reviewed all clinical records of patients seen at the Snake River Health Service from January 1987 through March 1990. The records of patients with a clinical diagnosis of HAPE were collected and reviewed by two physicians to select patients who fulfilled the following diagnostic criteria: In the setting of a recent gain in altitude, the presence of at least two of the following symptoms: dyspnea at rest, cough, weakness or decreased exercise performance, chest tightness or congestion, and an abnormal chest film showing a definite pulmonary infiltrate or an abnormal degree of vascular congestion. The symptoms criteria are based on the Lake Louise consensus on the definition of altitude illness.[4]

All patients had a history taken and a physical examination with entry of data into a standard medical record. An Omheda 3740 pulse oximeter was used to record the heart rate and fingertip arterial oxygen saturation. Blood pressure was determined by sphygmomanometry, and the respiratory rate and oral temperatures were recorded. All patients received a standard 6-ft posteroanterior chest radiograph during held inspiration. Chest films were reviewed by three physicians who were unaware of the clinical findings. For estimating the amount of infiltrate, the lungs were divided into four quadrants. The size of pulmonary infiltrate was estimated and reported in five grades according to the estimated area of the infiltrate: 0.5 = area of less than one quadrant, 1 = area equal to one quadrant, and 4 = all four quadrants involved. Special findings such as cardiac enlargement, pleural fluid, or Kerley B lines were recorded when present.

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Data Analysis

All raw data were entered into master charts and then entered into a computer for analysis using the EPI-INFO and SPSS+ PC programs. Between-group differences with parametric data were examined by analyses of variance and Student's *t* tests. Categorical data were analyzed using the Kruskal-Wallis test. Standard deviations are presented with the mean values. Statistical difference was reported when the *P* value was less than .05.

Results

A total of 166 patient records were reviewed, and 16 were excluded for the following reasons: 2 had no chest radiographs; 2 had cardiac failure; 3 had acute mountain sickness with a normal chest film; and 11 had conditions other than HAPE, including bronchitis, pneumonitis, flu, hyperventilation, and anxiety.

Day of Onset

The mean time from arrival to the day of the onset of symptoms was 3 ± 1.3 days (range, 1 to 9). Patients younger than 19 years became ill slightly sooner after arrival at altitude, a mean of 2.6 ± 1.0 days compared with a mean of 3.1 ± 1.3 days for those 20 or older. This difference approached, but did not reach, statistical significance.

Age

The mean age of all patients was 34.3 ± 15.5 years—range, 4 years to 78 years. The age distribution is shown in Figure 1. Nearly half (46%) of patients were in the age group of 20 to 39 years. This is comparable to the age distribution of 3,158 adult visitors to the area evaluated elsewhere, in which 41% of the visitors were 20 to 39 years of age.[1] Of the patients in the current study, 19% were 4 to 19 years of age. This suggests a greater incidence of HAPE in the young, which has been previously described.[5] High-altitude pulmonary edema did not appear to be more severe in younger patients, however. Patients aged 19 years or younger had a radiographic score of 1.5 ± 1.1, which is not significantly different from the mean radiographic score of older adults of 1.4 ± 1.1 ($P = .73$).

Sex

Men constituted 84% of the patients, and women accounted for only 16%. The mean age of the women was 35.5 ± 17.8 years, which is not different from that of the men (34.3 ± 14.9 years; $P = .73$) (Figure 1). Of the women, 21% were 50 years or older compared with 12.2% of men ($P = .5$).

Symptoms

All symptoms recorded at the time of clinic entry are shown in Table 1. The most common symptoms were dyspnea, cough, chest congestion, nausea or vomiting, and headache. A total of 126 (84%) had three or more symptoms, 18 had two symptoms, and only 6 had one symptom. Of the 24 patients with only two or fewer symptoms, 22 had one symptom characteristic of HAPE, including chest tightness, dyspnea, or cough. Chills, fever, or sweats were present in 30%, and 21% complained of poor sleep. Orthopnea was present in 10 patients who complained of dyspnea—an incidence of 9%. Chest pain or syncope was rare, occurring in only two patients. Only 10% of patients with cough had hemoptysis.

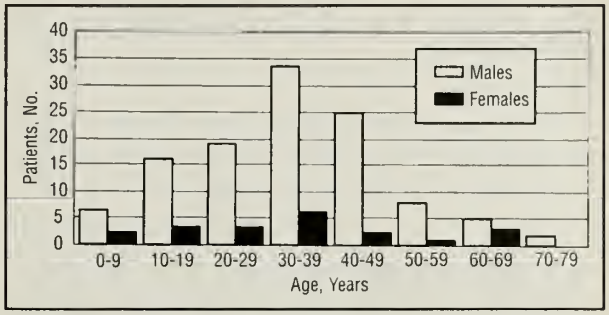

Figure 1.—The age-sex distribution of 150 patients with high-altitude pulmonary edema is shown. The mean age is 34.5 years.

Heart Rate

A rapid heart rate was common. The mean heart rate was 104.2 beats per minute. Heart rates of 120 per minute or more were recorded in 40 patients (26.7%), and only 13 (10%) had heart rates of less than 80 per minute.

Respiratory Rate

The mean respiratory rate was 22.9 ± 6.2 per minute; 39 (26%) had a rate greater than 24 per minute.

Temperature

The mean temperature was 99°F ± 1.45°F. Temperatures exceeding 100°F occurred in 30 patients (20%). There was no significant difference in chest radiograph

TABLE 1.—*Major Symptoms of High-Altitude Pulmonary Edema in Patients at a Rocky Mountain Ski Area (n = 150)*

Symptom	Patients, No	%
Dyspnea	115	77
With orthopnea	11	7.3
Cough	103	69
With hemoptysis	9	6
Headache	80	53
Chest congestion	62	41
With sounds of fluid	8	21
Nausea	52	35
With vomiting	24	16
Feverish chills, sweats	45	30
Weak, fatigue	38	25
No sleep	32	21
Dizzy, lightheaded	25	17
Confusion, lethargy, drowsy, disoriented	21	14
Ataxia	3	--
Malaise	17	11.3
Palpitation	14	9.3
Aches	5	1.0
Chest pain	1	--
Syncope	1	--

scores or oxygen saturation between those with a fever and those without.

Blood Pressure

The mean systolic blood pressure was 132.4 ± 19.9 mm of mercury (range, 88 to 200). In all, 26 patients (17.3%) had a systolic blood pressure of 150 mm of mercury or higher. The mean diastolic pressure was 84 ± 13.07 mm of mercury; 18 (13%) had a diastolic pressure of 100 mm of mercury or higher. Blood pressures of 150/90 mm of mercury or higher were recorded in 17 patients (12.0%). A blood pressure of 150/90 mm of mercury or higher was more common in older patients; 17 patients with this degree of hypertension had a mean age of 42.1 years compared with the mean age of 34.3 years for all patients. Although systolic blood pressures were higher in older patients, diastolic pressures were not. In 19 patients older than 50 years, the mean systolic pressure was 141.8 mm of mercury compared with 130.2 mm of mercury for patients aged 50 or younger. The mean diastolic pressure was 81.4 mm of mercury compared with 84.9 mm of mercury for patients aged 50 or younger.

Rales

Rales were present in 127 patients (85%) and absent in 23 patients (15%). Most rales were bilateral (55%) or only on the right side (24%). Nine patients (6%) had only left-sided rales.

Radiologic Features

A pulmonary infiltrate was present in 132 patients (88%). Most of the infiltrates were bilateral involving the central portion of both lung fields. This was the case in 80 patients (53%). The right mid-lung field only was involved in 51 patients (34%), and only 1 patient had a single infiltrate in the left lung. Infiltrate was absent in 18 patients (12%), but an abnormal degree of vascular congestion was present in each of their chest radiographs.

Grading of the chest films revealed the scores shown in Table 2. Nearly half the films (47.2%) were graded 0.5 and 1.0, which represents a relatively mild degree of pulmonary infiltrate. Only seven (4.7%) had involvement of all four lung fields. The mean score of all 133 films with infiltrates was 1.42. A typical chest radiograph is shown in Figure 2.

The absence of rales did not correlate with a lower infiltrate radiographic score. The mean radiographic score of 23 patients without rales was 1.1 compared with a mean score of 1.5 for 127 patients with rales ($P = .15$). If rales were present bilaterally, the radiographic score was slightly higher (mean, 1.6) than if rales were present on only one side (mean, 1.2; $P = .06$), but this is probably not clinically significant.

Pulse Oximetry

Arterial oxygen saturation was determined in 45 patients breathing room air. The mean saturation was 74.4% (range, 38% to 93%). The mean value for recent arrivals at 2,500 m (8,200 ft) is 92% (± 1.0%).[6] The mean score of 35 patients with saturations below 70% was 2.8, whereas the mean score of 22 patients with saturations above 80% was 1.4. Bilateral rales were more common, 12 of 12 (100%), in patients with saturations below 70% compared with only 7 of 15 (46%) in patients with a saturation of greater than 80%.

Figure 2.—A chest film was taken of a 29-year-old man in whom high-altitude pulmonary edema developed 4 days after arrival at high altitude. The infiltrate in the left lower lung field represents a radiologic score of 1.0.

High-Altitude Cerebral Edema

Five patients had clear clinical signs of high-altitude cerebral edema. Major symptoms were ataxia, lethargy, confusion, and disorientation. One patient had retinal hemorrhages. In 15 other patients, mental changes probably represented cerebral edema. These symptoms consisted of lethargy in 6, disorientation in 11, and somnolence, listlessness, and slowed reaction in 5.

Repeat Pulmonary Edema

Second episodes of pulmonary edema were rare in this study population. One patient gave a history of an episode of HAPE two years previously, and one said he had experienced "altitude sickness" during a previous exposure to high altitude.

TABLE 2.—*Distribution of Severity Grades in Chest Radiographs in Patients With High-Altitude Pulmonary Edema*

Grade	Patients, No.	%
B, Moderate vascular congestion	2	1.3
C, Definite vascular congestion	17	11.3
0.5	34	22.7
1	37	24.7
2	31	20.7
3	22	14.7
4	7	4.7

Reentry High-Altitude Pulmonary Edema

A 7-year-old boy, a resident of Frisco, Colorado (altitude 2,837 m [9,300 ft]), returned from a 20-day vacation at sea level, and severe dyspnea developed two days after he returned to altitude. His respiratory rate was 42 per minute, heart rate 128 beats per minute, and bilateral basal rales were present with an x-ray film score of 2.0. The arterial oxygen saturation was 74% with the patient breathing room air. A telephone survey of 32 patients with an initial history of HAPE revealed no instances of reascent HAPE.[7] Thus, in this group reascent HAPE appears to be rare.

Spinal Scoliosis—A Risk Factor?

Another observation of interest is the occurrence of HAPE in two persons with severe spinal scoliosis. Severe dyspnea and chest congestion developed in a 13-year-old girl 24 hours after she arrived at Keystone from Golden, Colorado (altitude 1,739 m [5,700 ft]). Her temperature was 96.7°F, respiratory rate 44 per minute, and heart rate 124 beats per minute. Bilateral rales and infiltrates were present. The radiologic score was 3.0 (Figure 3).

Dyspnea and malaise developed in a 31-year-old man from Texas seven days after he arrived at Keystone. His blood pressure was 122/98 mm of mercury, respiratory rate 32 per minute, and heart rate 114 beats per minute. Rales and infiltrates were present bilaterally, with an x-ray film score of 2.0.

Both patients were referred to a Denver hospital. Scoliosis interferes with respiratory function by restricting lung volume, resulting in alveolar hypoventilation, hypoxemia, and pulmonary hypertension. Sleep hypoxemia may be exaggerated.[8] Unilateral HAPE has been described in a patient with hypoplasia of the right pulmonary artery.[9] These abnormalities may predispose patients with scoliosis to HAPE in much the same manner as congenital absence of the right pulmonary artery.[10]

Figure 3.—High-altitude pulmonary edema occurred in a 13-year-old girl with severe spinal scoliosis in whom symptoms developed 24 hours after arrival from an intermediate altitude of 1,739 m (5,700 ft).

Treatment Methods

After initial treatment with oxygen, the following five methods were employed in the patients included in this report: descent to a Denver hospital (19%), return to living quarters with portable oxygen (18%), overnight stay at the Summit County Medical Clinic for oxygen therapy and monitoring (14%), return to quarters to observe rest for 24 to 48 hours (7%), or descent to a lower altitude (41%). There were no complications or deaths.

Discussion

Few systematic studies have been made of HAPE at Colorado ski resorts. The clinical features of 46 patients seen at the Vail (Colorado) Hospital from 1975 to 1982 have been described.[2,3] All patients recovered promptly without complication or death. Most of the essential features in this study were comparable to those described in those reports, including age, sex distribution, day of onset, and occurrence during the winter months. Vital signs including heart rate, respiratory rate, temperature, and blood pressure were also comparable to those reported earlier.

Several aspects of the current study deserve discussion: HAPE appears to occur more frequently in men than in women.[2,3,11] The gender difference, however, can be determined only if the age distribution of the group at risk is known. In another study, 3,158 adults attending conferences in Rocky Mountain ski resorts from July 1989 to May 1991 were interviewed; 69% were men.[1] At the ski area where this study was done, 54.6% of the skiers were men. Of 46 patients seen at Vail with HAPE, 43 (93%) were men.[3] The 84% incidence of HAPE in men thus represents a greater susceptibility of men than women to HAPE. The lower incidence of HAPE in women may be due to a greater increase in pulmonary ventilation at high altitude. Elsewhere it was shown that women brought to Pikes Peak (4,300 m [14,104 ft]) had a higher arterial Po_2 and bicarbonate concentration than men.[12] The effect on ventilation is probably due to estrogen and progesterone.[13] Arterial oxygen unsaturation during sleep occurs more frequently in men than in women.[14] Subjects with a history of HAPE have a blunted hypoxic ventilatory drive.[15]

The symptoms of HAPE were multiple in most instances and included characteristic symptoms of dyspnea, cough, headache, or chest tightness or congestion. Orthopnea was rare, occurring in 9.6% of 115 patients with dyspnea. Hemoptysis occurred in only 8.7% of 103 patients with cough. In all, 20 patients (13.3%) had some mental changes suggestive of high-altitude cerebral edema, 5 of whom had ataxia.

Vital signs included a moderate degree of temperature elevation and the frequent presence of systemic hyperten-

sion. Of the patients, 20% had a temperature exceeding 100°F. An oral temperature of 99.9°F should be taken as the upper limit of normal in healthy adults aged 40 years and younger.[16]

The presence of temperature elevations has been reported in patients with HAPE but not in patients with acute mountain sickness.[17] Possible explanations are the release of thermogenic proteins from fibrin deposition in the lungs and an increase in sympathetic nervous system activity, including high blood levels of norepinephrine.[18,19] This is accompanied in many patients by leukocytosis and elevated serum enzyme levels.[20]

The frequent finding of elevated blood pressures is probably the result of the hypoxia of HAPE and the presence of high levels of norepinephrine that has been reported by others.[18,19] It is of interest that elevated blood pressures were not found in 97 soldiers with HAPE at 3,508 m (11,500 ft). None had a systolic pressure of higher than 140 mm of mercury, and none had a diastolic pressure higher than 100 mm of mercury compared with 17% and 18%, respectively, in the current study.[21]

A common physical finding in HAPE is the presence of rales. In this study, rales were present in 85% of patients. Most were bilateral or only on the right side. It should be noted that 15% of patients had no rales despite an abnormal chest x-ray film. Radiologic features consisted of a pulmonary infiltrate in 78% of patients, largely involving both lung fields. The severity grading system used indicated that most patients had only a mild or moderate degree of HAPE. Only about 19% had an infiltrate involving three or four lung quadrants. About 13% of patients had no pulmonary infiltrate but had an abnormal degree of vascular congestion. In these patients, the clinical findings, including the presence of rales, was similar to those in patients with infiltrates. Similar findings have been reported elsewhere.[22,23]

Treatment methods required the use of an ambulance to descend to a Denver hospital in only 19% of patients who had more severe HAPE. Mild cases recovered simply by descent to a lower altitude. Of the total cases, 39% were treated without leaving the area by receiving oxygen or bed rest in their living quarters or an overnight stay at a local clinic. In these patients, it was not necessary to cancel often a long-planned vacation. Bed rest alone without descent or oxygen has been shown to result in recovery in mild cases of HAPE.[24] Nifedipine has been used in therapy, employing an initial dose of 10 mg sublingually followed by 30 mg of slow-release nifedipine twice a day. Nifedipine use has been shown to relieve symptoms of HAPE, to lower pulmonary artery pressure and resistance, and to increase arterial oxygen saturation.[25,26] It has also been shown to prevent HAPE in susceptible subjects.[27] Other therapeutic measures have been discussed elsewhere.[28]

The current study has several limitations. It is a retrospective study, and not all clinical symptoms may have been listed in the patient records by the admitting physician. Sea-level and recovery values for blood pressure are not available; hence, the high values observed cannot be definitely attributed solely to the effect of HAPE. By requiring an abnormal chest roentgenogram as a diagnostic criterion for HAPE, some patients with HAPE may have been excluded who had clinical symptoms and signs but who had a normal chest film. The routine use of a chest roentgenogram in patients with suspected HAPE may not be necessary if symptoms are mild and if rales and a low arterial oxygen saturation are present. Most physicians, however, use routine chest films to confirm the diagnosis, estimate severity, decide on therapy, and rule out other pulmonary conditions such as pneumonia that may stimulate HAPE.

Conclusion

High-altitude pulmonary edema occurs at ski resorts above 2,440 m (8,000 ft), with several cases seen per year at each resort area medical facility in this altitude range. Dyspnea, cough, chest congestion, and weakness occurring two to four days after arrival from a lower elevation is characteristic. An increased heart rate and respiratory rate are common, and a slight temperature elevation may be present. The systolic blood pressure may be elevated. Cerebral dysfunction manifested by lethargy, confusion, or disorientation may be present, and signs of cerebral edema may occasionally be noted. The diagnosis is confirmed by the presence of rales, a pulmonary infiltrate by chest x-ray film, and a low oxygen saturation by pulse oximetry. Rapid improvement usually results after two hours of breathing 100% oxygen and the administration of nifedipine. Mild cases with minimal symptoms will usually recover after a day or two of bed rest and limited activity or descent to a lower altitude. Moderately severe cases may be admitted to a local facility or return to their living quarters for bed rest, continuous low-flow oxygen by nasal prongs, and taking nifedipine twice a day. Severe cases with pronounced incapacity will require either admission to a local hospital or travel by ambulance to a medical center at a lower altitude.

REFERENCES

1. Honigman B, Theis MK, Koziol-McLain J, et al: Acute mountain sickness in a general tourist population at moderate altitudes. Ann Intern Med 1993; 118:587-592

2. Sophocles AM Jr, Bachman J: High-altitude pulmonary edema among visitors to Summit County, Colorado. J Fam Pract 1983; 17:1015-1017

3. Sophocles AM Jr: High-altitude pulmonary edema in Vail, Colorado, 1972-1982. West J Med 1986; 144:569-573

4. Lake Louise Consensus on the definition and quantification of altitude illness, *In* Sutton J, Coates G, Houston C (Eds): Hypoxia and Mountain Medicine. Burlington, VT, Queen City Printers, 1992, pp 327-330

5. Hultgren HN, Marticorena E: High altitude pulmonary edema—Epidemiologic studies in Peru. Chest 1978; 74:372-376

6. Roach RC, Houston CS, Honigman B, et al: How well do older persons tolerate moderate altitude? West J Med 1995; 162:32-36

7. Campbell J, Honigman B, Nicholas R, Stelzner T: The recurrence of pulmonary edema in visitors to moderate altitude (Abstr). Clin Res 1992; 40:42A

8. Iber C, Ingram Jr: Disorders of the chest wall, chap 7, *In* Scientific American Medicine. New York, NY, Scientific American, 1991, pp 3-4

9. Fiorenzano G, Rastelli V, Greco V, Di Stefano A, Dottorini M: Unilateral high-altitude pulmonary edema in a subject with right pulmonary artery hypoplasia. Respiration 1994; 61:51-54

10. Hackett PH, Creagh CE, Grover RF, et al: High-altitude pulmonary edema in persons without the right pulmonary artery. N Engl J Med 1980; 302:1070-1073

11. Hochstrasser J, Nanzer A, Oelz C: [Altitude edema in the Swiss Alps: Observations on the incidence and clinical course in 50 patients.] Schweiz Med Wochenschr 1986; 116:866-873

12. Hannon J: Comparative adaptability of young men and women, *In* Folinsbee L, Wagner J, Borgia J, Drinkwater B, Gliner J, Bedi J (Eds): Environmental Stress: Individual Human Adaptation. New York, NY, Academic Press, 1978, pp 335-350

13. Regensteiner JG, Woodard WD, Hagerman DD, et al: Combined effects of female hormones and metabolic rate on ventilatory drives in women. J Appl Physiol 1989; 66:808-813

14. Block AJ, Boysen PG, Wynne JW, Hunt LA: Sleep apnea, hypopnea and oxygen desaturation in normal subjects—A strong male predominance. N Engl J Med 1979; 300:513-517

15. Matsuzawa Y, Fujimoto K, Kobayashi T, et al: Blunted hypoxic ventilatory drive in subjects susceptible to high-altitude pulmonary edema. J Appl Physiol 1989; 66:1152-1157

16. Mackowiak PA, Wasserman SS, Levine MM: A critical appraisal of 98.6°F as the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. JAMA 1992; 268:1578-1580

17. Maggiorini M, Bärtsch P, Oelz O, et al: Elevated body temperature in severe mountain sickness (AMS) (Abstr), *In* Sutton J, Coates G, Houston C (Eds): Hypoxia and Mountain Medicine. Burlington, VT, Queen City Printers, 1992, p 311

18. Reeves J, Moore L, Wolfel E, et al: Activation of the sympatho-adrenal system at high altitude, *In* Veda G, Reeves J, Sekiguchi M (Eds): High Altitude Medicine. Matsumoto, Japan, Shinshu University Press, 1992, pp 10-23

19. Wolfel EE, Selland MA, Mazzeo RS, Reeves JT: Systemic hypertension at 4,300 m is related to sympathoadrenal activity. J Appl Physiol 1994; 76:1643-1650

20. Kobayashi T, Koyama S, Kubo K, Fukushima M, Kusama S: Clinical features of patients with high-altitude pulmonary edema in Japan. Chest 1987; 92:814-821

21. Menon N: High-altitude pulmonary edema—A clinical study. N Engl J Med 1965; 273:66-73

22. Vock P, Fretz C, Franciolli M, Bärtsch P: High-altitude pulmonary edema: Findings at high-altitude chest radiography and physical examination. Radiology 1989; 170:661-666

23. Vock P, Brutsche MH, Nanzer A, Bärtsch P: Variable radiomorphologic data of high altitude pulmonary edema—Features from 60 patients. Chest 1991; 100:1306-1311

24. Marticorena E, Hultgren HN: Evaluation of therapeutic methods in high-altitude pulmonary edema. Am J Cardiol 1979; 43:307-312

25. Oelz O, Maggiorini M, Ritter M, et al: Nifedipine for high altitude pulmonary oedema. Lancet 1989; 2:1241-1244

26. Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD: The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema—A comparison. Int J Sports Med 1992; 13(suppl):S68-S70

27. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, Oelz O: Prevention of high altitude pulmonary edema by nifedipine. N Engl J Med 1991; 325:1284-1289

28. Hultgren HN: High-altitude pulmonary edema—Current concepts. Annu Rev Med 1996; in press

* * *

Gallium Scan

Child, you play different games;
this one is white cell hide-and-seek,
medical isotope tag.
Worried parents whisper, "Hush, hold still,"
and position your small body
on the cold, long table,
a reluctant loan to foreign gods.

Each morning for three days
they keep appointments
with our long table,
with that scanning machine
where your leukocyte stars sparkle
on the overhead screen
as we track gallium-tagged white cells
to secret places
in the temporary universe of your young body.

Yet in the end
huddled radiologists
name no new heavens.

STEPHANIE PERSHING BUEHLER, MT (ASCP)©
Big Horn, Wyoming

Articles

Do Premedical Students Know What They Are Getting Into?

JOHN M. CHUCK, MD, *Fairfield, California*

The number of medical school applications continues to rise despite recent reports of decreased physician job satisfaction. To better understand this paradoxical trend, I surveyed 84 premedical students about their expectations of a medical career. Almost all respondents anticipated that as physicians they would be able to cure, heal, and help their patients (98%) and that their work would be intellectually satisfying (95%). Most anticipated that their jobs would be prestigious (83%) and even fun (73%). Far fewer than half the respondents would be discouraged from pursuing a medical career by the fear of being sued (38%), business worries (22%), or administrative duties (20%). Comparison of the student responses with results of a physician job satisfaction survey carried out the same year showed that the students, as a group, were modestly idealistic with respect to the daily work of being a physician and somewhat naive about the problems caused by various business and administrative issues. I conclude that premedical students could be better informed about the current reality of being a physician and that practicing physicians are responsible for providing this education.

(Chuck JM: Do premedical students know what they are getting into? West J Med 1996; 164:228-230)

Given the current state of physician job satisfaction, it is somewhat puzzling that applications to United States medical schools numbered an all-time high of 45,365 in 1994 (M. Frase-Blunt, Washington, DC, oral communication, 1995). Physicians seem to be complaining more than ever about their profession. Gallup polls conducted for the American Medical Association in 1989 and 1990 showed that only 60% of physicians interviewed would definitely or probably enter medical school again.[1] Medical journals are filled with physicians writing about how the "fun" has been taken out of medicine and how physicians are no longer considered "special."[2,3] In forums ranging from *The New York Times* to backyard barbecues, physicians are complaining about increased paperwork and decreased income, regulatory agencies interfering with physician autonomy in decision making, and deterioration in the physician-patient relationship. Further, medical education costs have risen so that the typical medical school graduate now incurs an average debt of at least $50,000.[4,5] In addition, the ability to pay back this debt has been hampered by the lengthening of some residency and fellowship programs, decreased salaries for fellows in saturated subspecialties, and decreased salaries for physicians overall, especially those in subspecialty fields, which often require the most years of training.

For a record number of students to apply to medical school under these circumstances raises the question: "Do premedical students know what they are getting into?" Nationwide, only a handful of formal programs specifically provide students with extended, meaningful exposure to medical care and practice.[6] Most premedical students are left to formulate a concept of the reality and demands of the medical profession through a patchwork of hospital volunteer work, research experience, talking with whatever physicians they come in contact with—often those in academic settings who are not primarily involved in patient care—and counseling from premedical advisors, few of whom are physicians. To partially answer this question, I surveyed a group of premedical students about their expectations of what a medical career would be like and then compared their responses with a concurrent job satisfaction survey of practicing physicians in the immediate geographic area.

Methods and Study Group

From January through June 1992, 84 premedical students attending premedical society meetings or counseling sessions at two San Francisco Bay Area universities (University of California at Berkeley and California State University at Hayward) were given a questionnaire designed to assess the factors that influenced their decision to pursue or not to pursue a career in medicine and their expectations regarding such a career. The questionnaire items were rated on a scale from 1 ("disagree strongly") to 7 ("agree strongly"), with 4 representing "neutral." The responses from this study group were compared with those from a group of practicing physicians in nearby Solano County.

Results

All 84 students completed the questionnaire. Student respondents were a mean age of 22 years; 48 of them

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TABLE 1.—*Respondents Who Agreed With Positive Expectations About Physician Career*

Expectations	*Students Agreeing, No. (%) n = 84*	*Practicing Physicians Agreeing, % n = 251*
Would be able to cure, heal, help patients	82 (98)	92
Work would be intellectually satisfying	80 (95)	89
Job would be prestigious	70 (83)	63
Work would be fun	61 (73)	63
Earnings would be satisfactory	71 (84)	72
Would have control over hours night, weekend duty	20 (24)	47*
Meaningful personal and family life	53 (63)	83

*Of 251 physicians in practice, 60% were satisfied with their weekend and night duty.

were women (57%), and 36 were men (43%); 73 respondents were single (87%), 8 were married (10%), and 3 were divorced (4%).

Most respondents indicated that their interest in being a physician had been positively influenced by exposure to a role model (60 [71%]), by their parents (56 [67%]), or both. About half of the respondents indicated their interest had been positively influenced by their peers (44 [52%]).

Most students had positive expectations about their lives as physicians (Table 1). Almost all the respondents indicated that they anticipated as physicians that they would be able to cure, heal, and help their patients (82 [98%]) and that their work would be intellectually satisfying (80 [95%]). In addition, most anticipated that their job would be prestigious (70 [83%]), even "fun" (61 [73%]), and that they would be satisfied with their earnings (71 [84%]). Only 20 (24%) expected to have control over their hours and night and weekend duty.

Students rated each of several possible factors that might discourage them from pursuing medical careers (Table 2). About half the respondents indicated that the time commitment of medical school and residency (47 [56%]), the financial cost of the same (44 [52%]), the mental stress of being a physician (43 [51%]), and the fear of making a mistake (39 [46%]) might seriously discourage them from pursuing a career in medicine.

Fewer students indicated that the physical stress of being a physician (36 [43%]), the high cost of malpractice insurance (34 [40%]), and the fear of being sued (32 [38%]) might also discourage them from medical careers. Finally, even fewer respondents indicated that the fear of contracting a serious disease (such as the acquired immunodeficiency syndrome) (23 [27%]), business worries (18 [21%]), and administrative duties (17 [20%]) might discourage them from pursuing medical careers.

Other factors that might discourage the student respondents from medical careers were highlighted by the following verbatim comments: "I find the attitudes of many of my peers [that is, "anything for an A"] fairly disturbing"; "If I have to change, become a harder, self-centered person to survive, I won't go"; "I worry about the impact [of my decision to go into medicine] on my personal life and sacrificing my family for my career"; "Western medicine has lost its humanity"; "[I'm concerned about] sexism and ageism in the medical establishment"; "What if the work is not satisfying? Then all the years of education [would have been] wasted."

Student Expectations Versus Reality

In the same year (1992), 406 practicing physicians in nearby Solano County were sent a job and career satisfaction questionnaire to which 251 responded (62%). Results of that survey were published in an earlier issue of this journal.[7] When compared with these physicians' responses, the students' expectations of their medical careers were modestly idealistic on issues related to the daily work of being a physician and overly pessimistic with respect to lifestyle issues.

As a group, our student respondents underestimated the negative toll that various business and administrative issues have taken on practicing physicians (Table 2).

Discussion

During these times of rapid change in the medical profession, even physicians cannot clearly define and evaluate their own profession because issues related to autonomy, the physician-patient relationship, and reimbursement are in flux. Those outside the profession, including premedical students, are also confused.

During such uncertain times, a decline in interest in medical careers and in the number of applications to medical school would be expected. Yet, the number of applications to medical school continues to increase greatly. The results of my survey suggest that this may partly be due to premedical students being overly idealistic and naive about what their lives as physicians will be like. A more meaningful reason for this increase, however, may be that when numerous careers are

TABLE 2.—*Respondents Who Agreed With Listed Factors That Might Discourage Them From Pursuing Medical Careers*

Factor	Students Agreeing, No. (%) n = 84		Practicing Physicians Agreeing These Were Problems, % n = 251
Time commitment to medical school and residency	47	(56)	*
Financial cost	44	(52)	†
Mental stress	43	(51)	‡
Physical stress	36	(43)	‡
High cost of malpractice insurance	34	(40)	67
Fear of being sued	32	(38)	§
Fear of contracting a serious disease	23	(27)	45
Business worries	18	(21)	28
Administrative duties	17	(20)	34

*Of the 251 physicians, 65% agreed the time commitment was worthwhile.

†Of the 251 physicians, 61% agreed the financial cost was worthwhile.

‡No similar questions were posed to practicing physicians.

§Of the 251 physicians, 58% agreed the fear of being sued adversely affected the way they practiced medicine.

carefully compared, medicine continues to offer a relatively appealing combination of professional satisfaction and financial security.

What is clear is that regardless of the reasons for the increase in medical school applications, those students considering medical careers and those who actually apply could make more informed career decisions if they better understood the day-to-day realities of medical practice. The responsibility to share this information rests on practicing physicians. Opportunities to educate students about medical careers include individual preceptorship or "shadow" arrangements, volunteering to counsel students through college preprofessional offices, speaking at high school and college premedical clubs, and organizing or participating in extended formal programs. When engaging in such activities, physicians must present an honest portrayal of their work and emphasize both the positive and negative aspects of what they do, especially because this study and others have explicitly shown that physician role models can positively and negatively influence students' decision to pursue or not to pursue a medical career.

Acknowledgment

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REFERENCES

1. Harvey LK, Shubat SC: Physician and Public Attitudes on Health Care Issues. Chicago, Ill, American Medical Association, 1989

2. Lacsamana RG: Quitting when the fun is gone (Editorial). J Fla Med Assoc 1988; 75:789

3. Kopitnik NL: Whose fault is it doctors aren't 'special' anymore? Med Econ 1992; 69:183-186

4. Rosenthal MP, Diamond JJ, Rabinowitz HK, et al: Influence of income, hours worked, and loan repayment on medical students' decision to pursue a primary care career. JAMA 1994; 271:914-917

5. Richardson M: Burden of debt: Loans often influence specialty choice of medical school graduates. Texas Med 1994; 90:26-29

6. Alexander SF, Lyon LJ, Nevins MA, Yere LR Jr, Thayer HS: Ten years of orienting college students to careers in medicine. JAMA 1992; 267:3330-3331

7. Chuck JM, Nesbitt TS, Kwan J, Kam SM: Is being a doctor still fun? West J Med 1993; 159:665-669

Articles

Snowboarding Injuries

A Four-Year Study With Comparison With Alpine Ski Injuries

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Snowboarding is a rapidly growing winter sport. Its unorthodox maneuvers and young participants raise many safety concerns. We examined injury patterns in recreational snowboarders, comparing these patterns with those found in alpine skiers. Snowboarding and skiing injury patterns differed significantly ($P < .05$) for the following categories: 49% of injured snowboarders were beginners versus 18% of skiers. Snowboarders were more likely to suffer wrist (19% versus 2%) and ankle (16% versus 6%) injuries, but less likely to sustain knee (17% versus 39%) or thumb (2% versus 4%) injuries than skiers. For snowboarders, wrist injuries were most common in beginners (30%), knee injuries in low intermediates (28%), ankle injuries in intermediates (17%), and shoulder or clavicle injuries in advanced snowboarders (14%). Most snowboarders (90%) wore soft-shelled boots, 73% of lower extremity injuries occurred to the lead-foot side, and 73% of wrist injuries occurred during backward falls; 67% of knee injuries occurred during forward falls. Of all injuries, 8% occurred while loading onto or unloading from a ski lift. The sport of snowboarding brings with it a different set of injuries from those seen in alpine skiing. The data focus attention on improvements such as wrist guards or splints, releasable front-foot bindings, and better instruction for beginner snowboarders to improve the safety of this sport. Finally, the data confirm that snowboarders and skiers may be safely combined on the same slopes.

(Davidson TM, Laliotis AT: Snowboarding injuries—A four-year study with comparison with alpine ski injuries. West J Med 1996; 164:231-237)

Despite initial concerns over safety and liability, snowboarding has grown into a major winter sport. Now welcome at most North American ski resorts, snowboarders with their baggy pants and flannel shirts are predicted to have grown from an estimated 100,000 North American participants in the 1989-1990 season[1] to an estimated 20% to 30% of all lift-ticket holders by the 1999-2000 season, according to the publishers of *Transworld Snowboarding* (written communication, March 1994). Their skateboard- and surfboard-like maneuvers, both on snow and in the air, strike fear and dismay into the hearts of traditional alpine skiers and raise concerns over issues of safety to self and others (K. Hamilton, "Culture Clash on the Slopes," *Newsweek* 1993, 2:51).[2] This project was designed to characterize snowboarding injury patterns and to determine what factors influence these injuries and whether snowboarding and alpine skiing are compatible sports.

The first snowboards were called "snurfers" and were designed and developed by Sherwin Popper during the 1960s in Michigan (P. Shelton, "Riding a New Wave," *Skiing* 1988 Spring, 40:108-111, 127; P. Shelton, "I Surfed the Rockies," *Powder* 1987, 15:88-94; and E. Blankman, "Boards Ablaze," *Powder* 1987, 15:95-100, 120).[1] These first boards were made of wood with a skegg or fin on the bottom to help the board track in deep powder. Snurfers lacked the steel edges necessary for turning control on packed snow.[2] In the late 1970s, these difficult-to-control boards gave way to the "winterstick" by Dimitrije Milovich and later to the modern snowboards designed by Jake Burton Carpenter and Tom Sims.[1-3] Modern snowboards are constructed much like alpine skis, with fiberglass bodies, plastic bases, and steel edges, making them easier and safer to control on today's groomed ski slopes. Despite improvements in snowboard technology, many differences exist between ski and snowboard equipment.

Snowboarding boots can be divided into two types, hard and soft. Hard-shelled boots come in two varieties, the ski boot and the hybrid snowboard boot. Both hard-shelled boot varieties provide rigid ankle support, but the hybrid boot has a softer, more flexible upper for comfort and maneuverability.[4] The soft-shelled boots are the most popular among recreational snowboarders and consist of "sorrel" or sorrel-type boots manufactured by snowboarding companies. They provide less ankle support, allowing increased range of motion at the ankle for greater comfort and snowboard maneuverability. Hard inserts can be placed in the soft-shelled boot for increased ankle support; newer soft-shelled boots are being designed with stiffer ankle support. To date, most

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snowboard bindings are nonreleasing, in contrast to the multidirectional releasable binding used in alpine skiing.[5] The hard-shelled boot is fixed to the board by a metal plate or binding that is nonreleasable, whereas soft boots are held to the board by a soft, high-backed, buckle binding that is also nonreleasable. A final difference in equipment is that unlike skiers, snowboarders with their surferlike stance on the board do not use poles.

Along with differences in boot, board, and binding, the biomechanics of snowboarding are different from those of skiing. Snowboarders stand sideways on their boards, much as skateboarders or surfers do, with the rear foot at 90 degrees to the long axis of the board and the front foot positioned between 45 and 90 degrees to the long axis.[3,6] Turns are executed by shifting the body weight to the front foot and allowing the tail of the board to swing outward (Shelton, *Powder* 1987; N. A. Plate, "Snowboarding Only Looks Impossible," *Sunset* 1985 March, pp 78-82; and L. Han, "Snowboarding Basics," *Skiing* 1990, 43:204-212).[2]

Figure 1 shows two boarders executing the front and back turns typical of snowboarding. Without poles, the arms and hands are used more actively for maintaining balance and are often dragged along the snow surface for show or added stability. With the fixed bindings and sideways stance, the outstretched arms are often used to break a fall.[1] Snowboarders love to jump, as shown in Figure 2.

Although there is a substantial body of data characterizing alpine-skiing injuries, few data exist regarding snowboarding.[1,3,4,7-9] Published studies suggest that mechanisms and patterns of injury differ from those of traditional alpine skiers. Upper limb and ankle injuries are reported to be more common, and knee injuries are less common than in alpine skiers. One author reports that impact rather than torsion is the most common injury mechanism. Finally, it has been suggested that boot type influences the type and location of lower limb snowboarding injuries.[4,7] Missing from these studies has been a large-scale study that directly and statistically compares skiing and snowboarding injuries from the same ski area during the same seasons. Therefore, this study was designed to compare ski and snowboard injuries, characterizing differences in snowboard injury patterns and factors influencing these injury patterns. The second part of the study was designed to investigate the relationship of certain snowboard-specific factors such as boot type, activity, and lead foot with patterns and incidence of injuries.

Figure 1.—Two snowboard instructors demonstrate front and back side turns (photo courtesy of Brad Peatross, Mammoth Mountain Ski Area).

Figure 2.—Snowboarder jumping is shown. This is a frequent snowboard activity (photo courtesy of Brad Peatross, Mammoth Mountain Ski Area).

Methods

This study was designed in two parts. The first part reviews all injuries recorded during the 1989-1990 through the 1992-1993 ski seasons at the Mammoth and June mountains ski resorts (eastern Sierras, California). The second part was designed to prospectively look at factors influencing snowboarding injury patterns and took place during the 1989-1990 winter season. The study was conducted at the Mammoth-June ski resorts in California where the senior author (T.M.D.) has been a member of the ski patrol since 1963. During the four seasons of this study, the Mammoth-June ski area estimated that the number of snowboarders increased annually to an estimated 5% of all lift-ticket sales (written communication, December 1992).

The data for this project are taken from the incident-injury reports of the Mammoth-June Ski Patrol. All

diagnoses are made by winter emergency care-certified full-time professional ski patrollers. Patients self-triage to innumerable medical facilities, and physicians' diagnoses are simply not available. Fractures and sprains are distinguished by injury zone and patrol assessment; therefore, knee injuries, unless there is dislocation, are diagnosed as sprain, whereas a midshift lower leg injury is diagnosed as a fracture. The Mammoth-June Ski Patrol is responsible for completing incident reports on any injured person tended to by patrol or first-aid room staff at both Mammoth and June mountains. Completed incident reports are then entered into a computer accident file, including type of injury, body zone of injury, date and time of day, ability level, sex, age, snow and weather conditions, location of the accident, and whether the injured person was on a snowboard or skis. Snowboarders were first invited to the Mammoth ski area in the 1989-1990 season. The data reported here include the first four years' experience.

Data for the prospective snowboard study were collected during the 1989-1990 season in which ski patrol members completed a supplementary incident form on all snowboard incidents, including information on snowboard boot type; binding; snowboard length; snowboarder activity such as jumping, "riding the half-pipe," and getting on or off lifts; and lead foot and direction of fall such as toe side, heel side, and backward or frontward over the board.

Proportional data were compared among groups using the z test with Yates' correction.[10] Mean ages were compared using the unpaired Student's t test.[10] Statistical significance was accepted at P values of .05 or below.

Results

Part 1

Demographics. The total number of snowboarder injuries reported by the Mammoth-June Ski Patrol during the 1989 through 1993 seasons was 931. This compares with a total of 8,255 alpine skier injuries during the same time period. Total ticket sales for this period were 2,694,640. The percentage of these sold to snowboarders was not recorded. The average age of injured snowboarders was significantly lower than that of injured skiers (20.9 years versus 29.4 years, respectively) (Table 1). Of the 931 snowboarders injured, 72% were male, but only 48% of injured skiers were male. Injured snowboarders and skiers differed in their self-assessed ability level, with beginners comprising 49% of injured snowboarders versus 18% of skiers.

Cause of injury. Human error was the most common self-reported cause of injury in both snowboarders and skiers (60% and 58%, respectively). Equipment failures (0.54% and 1.46%) and speed (4.4% and 6.3%) were slightly more common among skiers ($P < .05$). Snowboarders were injured three times more frequently jumping than were skiers (15% versus 5%, $P < .001$). Collisions with objects, skiers, or snowboarders were the cause of injury more often in skiers than in snowboarders (14% versus 10%, $P < .002$), and only 1% of injuries to skiers were caused by collisions with snowboarders versus 7% of injuries to skiers being caused by collisions with other skiers ($P < .001$).

TABLE 1.—*Demographics of All Snowboarders and Skiers Injured During the 1989–1990 Through 1992–1993 Ski Seasons*

Chorocteristic	*Snowboorders*	*Skiers*
Total injuries, No.	931	8,255
Mean age (SD), years	20.9 (8.2)	29.5 (14.4)*
Sex		
Male, %	72	48*
Female, %	28	52*
Ability		
Beginner, %	49	18*
Low intermediate, %	7	14*
Intermediate, %	23	39
Advanced, %	15	18
Expert, %	5	4
Racer, %	1	2
Unknown, %	1	6

SD = standard deviation

*$P < .001$.

Injury zone. Compared with skiers, snowboarders sustained a higher percentage of upper extremity injuries (40% versus 17%), with fewer lower extremity injuries (38% versus 54%, $P < .05$) and axial or trunk injuries (17% versus 20%) (Table 2). The wrist was the most common site of injury to snowboarders, accounting for 19% of injuries. Other common snowboard injury sites included the knee (17%), ankle (16%), and clavicle or shoulder (10%). Compared with alpine skiers, snowboarders had significantly more injuries to their wrists (19% versus 2%, $P < .001$), arms (5% versus 2%, $P < .001$), elbows (2% versus 0.4%, $P < .001$), and ankles (16% versus 6%, $P < .001$). Snowboarders sustained significantly fewer injuries to their thumbs (2% versus 4%, $P < .002$), legs (5% versus 9%, $P < .001$), or knees (17% versus 39%, $P < .001$).

Injury type. The type of injury was evaluated and recorded by ski patrol and first-aid room staff without the aid of radiographic studies. Therefore, only first-aid impressions are reported. Snowboarders were twice as likely to sustain a fracture (27% versus 13%, $P < .001$). Snowboarders were less likely overall to sustain soft tissue or sprain or strain injuries than skiers. The rate of dislocations was identical in the two groups (5%), as was that of concussions (3%). There were no cases of hypothermia or death among the snowboarders and two cases of hypothermia and one death among skiers during the four seasons reported.

Most frequent injuries. Wrist injuries were the most common snowboarding injury at 19% versus 2% in alpine skiers. Knee injuries were the next most common injury reported in snowboarders (17% versus 39%). Ankle injuries were the next most reported snowboarding injury at 16% versus 6% in skiers. Thumb injuries

TABLE 2.—*Comparison of Most Common Injury Zones in Snowboarders and Skiers*

Injury Zone	Snowboorders, No. (%) n = 929		Alpine Skiers, No. (%) n = 8,046		P Volue
Upper extremity					
Shoulder	70	(8)	577	(7)	
Arm	45	(5)	194	(2)	<.001
Elbow	17	(2)	36	(0)	<.001
Wrist	176	(19)	182	(2)	<.001
Hand	18	(2)	94	(1)	
Thumb	21	(2)	361	(4)	<.002
Total	347	(37)	1,444	(18)	<.001
Lower extremity					
Thigh	1	(0)	32	(0)	
Knee	160	(17)	3,122	(39)	<.001
Leg	44	(5)	709	(9)	<.001
Ankle	148	(16)	458	(6)	<.001
Foot	4	(0)	9	(0)	<.05
Total	357	(38)	4,330	(54)	<.001
Axial skeleton					
Head and face	95	(10)	1,103	(14)	<.005
Neck or throat	9	(1)	89	(1)	
Chest or rib	16	(2)	120	(1)	
Back	24	(3)	249	(3)	
Clavicle	19	(2)	68	(1)	<.001
Hip or pelvis	9	(1)	119	(1)	
Total	172	(19)	1,748	(22)	<.05
Other	53	(6)	524	(7)	

were nearly half as common in snowboarders as in skiers (2% versus 4%). Shoulder or clavicle injuries are also common in snowboarders (8% and 7%).

Ability versus common injury zones. Among skiers, the knee was the most commonly injured area regardless of ability level. Among snowboarders, the most commonly injured area varied significantly among ability levels (Table 3). Beginning snowboarders were most likely to injure the wrists (30%), low intermediates their knees (28%), intermediates their ankles (17%), and advanced and expert snowboarders injured their shoulder or clavicle most commonly (14%).

Part 2

Demographics. Information for part 2 of the study was gathered on a prospective basis during the 1989-1990 season. Of the 210 snowboarders injured during the season, only 78 (37%) had correctly completed supplemental survey forms that could be used in the study. Many of the supplementary forms had to be excluded because of an inability to match the supplemental form with an incident reported in the accident database. There is no reason to think that these exclusions are not random, nor should they affect the outcome of this study. Demographics for this group did not vary significantly from all snowboarders for age, sex, or ability level.

Boot type. Of the 78 snowboarders, 70 wore the soft (sorrel or snowboard-specific) type boots. Only 1 of the 78 was reported wearing a snowboard-specific hybrid hard boot. Boot type was not reported for seven persons. Among the soft-boot wearers, there was no significant difference in injury patterns when comparing sorrel with snowboard brand-specific boots for any upper or lower extremity injury zones ($P > .15$). The one snowboarder wearing the hard hybrid boot sustained an injury to the ankle.

Lead foot. Of the 78 snowboarders, 41 (52%) rode with the left foot in the lead or forward position, whereas 36 (46%) snowboarded with the right foot forward. When we examined the correlation of injured side and lead foot, we found that upper extremity injuries had no predilection for lead or rear foot side (Table 4). Of the lower extremity injuries, however, 72% occurred to the lead foot extremity versus 28% to the rear foot extremity ($P < .001$). This difference was most noted for knee and ankle injuries but only significant for knee injuries (80% lead foot versus 20% rear foot, $P < .001$).

Activity. The most commonly reported activity leading to injury was "regular snowboarding," which included all facets of basic snowboarding maneuvers such as stopping, cruising, and standing. Turning was the next most frequent cause (21%). Together, turning and regular snowboarding maneuvers accounted for 53% of injuries, with reported mechanisms including simple falls to the slope as well as more complex falls with twisting and cartwheeling motions. Jumping accounted for 11 of the injuries among all snowboarders (14%) and was an especially common injury to the intermediate snowboarders (29%). Six injuries (8%) occurred during

TABLE 3.—*Comparison of Most Common Injury Zones by Ability Level for Snowboarders and Skiers**

Ability	Injury Zone %					
	Wrist	Arm	Shoulder	Knee	Leg	Ankle
Snowboarders						
Beginner	**30**	4	5	21	3	17
Low intermediate	11	6	6	**28**	5	20
Intermediate	11	8	7	13	7	**17**
Advanced or expert	6	4	**14**	9	6	10
Skiers						
Beginner	2	2	5	**49**	10	9
Low intermediate	1	2	5	**50**	10	6
Intermediate	2	3	8	**41**	9	5
Advanced or expert	3	3	10	**30**	9	4

*Bold numbers represent most common injury zone for each ability level.

lift loading or unloading, whereas speed (5 [6%]) and collisions (4 [5%]) accounted for relatively few injuries.

Direction of fall. Falls in the forward direction and during front-side turns were most common (42 [54%]), and falls backward and during heel-side turns were less common (26 [33%]). Table 5 shows that, when examining the direction of fall in relation to the three most common injury zones, knee and ankle injuries occur significantly more often during forward front-side-turn falls. Just the opposite is found for wrist injuries, with backward heel-side-turn falls being the direction of fall in 73% of wrist injuries reported.

Discussion

The results of this study show that snowboarders and skiers have substantially different injury patterns. Injured snowboarders were significantly younger and more likely to be male compared with skiers. This agrees with previous work showing a lower mean age (range, 19.6 to 21 years) and a higher percentage of men (range, 74% to 90%) in snowboarders compared with alpine skiers.[1,3,4,7,8] Beginners were the largest fraction of injured snowboarders both in this and previous reports.[1,4,7,8] Without controls, we cannot determine if any of the factors of young age, male sex, or beginner ability level are true risk factors for snowboard injuries. It has been noted that the overall population of snowboarders is relatively younger with more male participants than the skiing population (Hamilton, *Newsweek* 1993; Shelton, *Skiing* 1988; and Shelton, *Powder* 1987).[8] Although this new and growing sport should have a generous proportion of beginners, studies of alpine skiing injuries show beginners to have as much as a sixfold increase in risk of injury versus skiers of other ability levels.[11,12] Therefore, although it is less likely that age or sex are risk factors in snowboarding injuries, lower ability level may be an important risk factor for snowboarders. Because a breakdown of lift-ticket sales to snowboarders and skiers was not available, the overall incidence for snowboarding injuries could not be calculated. Other studies have estimated this rate to be between 2.0 and 4.2 injuries per 1,000 snowboarder days,[1,4,7] with one author estimating a higher rate at 8 to 16 injuries per 1,000 snowboarder days.[8] These estimates compare with recent calculations of an overall incidence of injury in alpine skiers of 3 to 6 injuries per 1,000 skier days.[5,12] In this study, it was noted that snowboarding accounted for about 10% of all injuries. During this same time period, the Mammoth-June ski resort management estimated that snowboarders accounted for 5% of all lift-ticket sales at the resort (written communication, December 1992). If these estimations are correct, then the overall injury rate in snowboarders at Mammoth-June ski resort may be twice that in skiers. As noted previously, the rapid growth of the sport has placed many beginner snowboarders on the slopes, some without formal instruction, and it would not be surprising if a somewhat higher overall incidence is noted and persists as the sport grows.

In this and another study, a low collision rate between snowboarders and skiers was demonstrated.[7] In fact, we found the collision rate between snowboarders and skiers to be lower than that for skiers colliding with skiers. Thus, any increased risk of injury to alpine skiers or snowboarders caused by sharing the same slopes has yet to be shown.

Another important finding in this study is the increased rate of upper extremity injuries when compared with skiers, a conclusion shared by other workers.[1,4,7] Wrist, arm, and elbow injury rates were all increased compared with those in skiers, and snowboarders were almost ten times as likely to injure the wrist as were their alpine skier counterparts. In fact, the wrist was the most common injury zone in the total population of injured snowboarders and accounted for a third of all injuries in beginning snowboarders. Differences in how a snowboarder falls may be responsible for the increased proportion of upper extremity injuries. As discussed, snowboards do not have releasable bindings, and poles are not used. During a fall, the feet remain fixed to the board, and the main force of impact with the snow is often placed on the outstretched arms. Figure 3 shows a snowboarder turning. Any slip

TABLE 4.—*Comparison of Injuries to Front Foot Side Versus Rear Foot Side Based on Injury Zone**

Injury Zone	Injured Side: Leod Foot, No. (%)	Injured Side: Reor Foot, No. (%)	P Volue
Upper extremity*	13 (52)	12 (48)	1.00
Lower extremity	23 (72)	9 (28)	<.001
Knee	12 (80)	3 (20)	<.001
Ankle	11 (65)	6 (35)	<.05

*Thumb, hand, wrist, elbow, arm, and shoulder injuries.

TABLE 5.—*Influence of Direction of Fall on Common Injury Zones*

Injury Zone	Direction of Foll*: Toe Side, No. (%)	Direction of Foll*: Heel Side, No. (%)	P Volue
Knee	10 (67)	3 (20)	<.05
Ankle	11 (65)	6 (35)	<.05
Wrist	4 (27)	11 (73)	<.05

*Falls forward or to the toe side of the board were classified as toe-side falls, and falls backward or to the heel side of the board were classified as heel-side falls.

could easily involve the upper extremities. Beginner snowboarders seem particularly at risk for wrist injuries, possibly reflecting a lack of knowledge of falling techniques that diminish the impact to the upper extremity or perhaps reflecting the increased number of falls suffered by beginning snowboarders.[1,4] In this study, injuries to the wrist were significantly more common during falls to the heel side of the snowboard, suggesting a greater force of impact to the upper extremity when falling backward.

Thumb injuries were significantly less prevalent than in alpine skiers in this and other studies.[3,4,8] Injuries to the thumb among skiers represent the most common upper extremity injury, with rupture of the ulnar collateral ligament, "skier's thumb," being the most common thumb injury.[13,14] The mechanism of injury described involves the ski-pole handle acting as a lever as the thumb collides with the snow during a fall, causing stretching or rupture of the ulnar collateral ligament.[13-16] Without poles, snowboarders seem to be at much less risk for thumb injuries.

Patterns in lower extremity injuries also differed among snowboarders and skiers, with knee injuries being twice as common in skiers and ankle injuries almost three times as common in snowboarders. Similar results have been reported in other studies, with speculation that the soft-shelled boot and the absence of release binding are the major contributing factors.[1,3,4,7,8] In this study, 70 snowboarders (90%) were found to be using the soft-shelled snowboarding boots, which provide less ankle stabilization, supporting our finding of an increased prevalence of ankle injuries. Other studies have shown that hard-shelled boots and soft boots with rigid ankle-support inserts substantially reduce the risk of ankle injuries, but increase the rate of knee injuries.[4,7] This pattern of injury in snowboarders is similar to that found in

Figure 3.—An extreme front-side turn is shown. The upper extremity is at obvious risk if the snowboarder falls (photo courtesy of Brad Peatross, Mammoth Mountain Ski Area).

the early years of skiing, when it was noted that the ankle was the most common injury zone in the lower extremity.[12] This pattern was attributed to the low-topped ski boots that provided little ankle support. As the boot became more rigid with a higher top to provide increasing ankle support, the rate of ankle injuries declined dramatically.[12] The dilemma is to better protect the ankle without adding increased risk to the knee. We conclude, as have others, that soft-shelled boots with rigid ankle inserts or supports, particularly in beginner snowboarders who have the highest incidence of ankle injuries, may be beneficial.[4,7] Further work needs to be done examining the effects of rigid inserts and soft boots with more rigid ankle support on the knee and ankle injury rates before more definitive recommendations can be made.

It was somewhat surprising to find that 72% of all lower extremity and 80% of knee injuries occurred to the leg in the front, or lead foot, position. Other workers have reported similar trends,[3,4,8] but this study is the first to show actual statistical significance. The reasons for this finding are unclear. It was initially thought that having both feet fixed to the snowboard would offer some protection from torsional injuries, particularly to the knees.[3] Although this study shows that snowboarders have fewer knee injuries than do skiers, the finding that most knee and lower extremity injuries are concentrated in the front foot suggests that different forces are acting on the front leg than on the rear leg. This may be due to the fact that the lead foot is usually placed at an angle of 30 to 45 degrees to the long axis of the board and not parallel to the rear foot. In a fall with the snowboard edge fixed in the snow and acting as a lever, the angle of the front foot may translate into different and possibly more damaging torsional forces acting on the lead leg. In addition, most of a rider's weight is concentrated on the lead foot when initiating a turn, thus placing greater forces on the front foot. Future attention needs to focus on the factors contributing to the preponderance of front-foot lower extremity injuries and perhaps the development of a release-binding system to protect the front foot.

Last, six of the snowboarder injuries (8%) occurred during loading and unloading from chairlifts. Chairlifts

have developed for the forward-facing two-skied alpine skier and may not be appropriate for the sideways-facing, one-foot-on-the-board snowboarder.

Conclusion

This study shows that the fast-growing sport of snowboarding has a notably different injury pattern from that seen in alpine skiing, with an overall incidence rate that is comparable to or higher than that for alpine skiers. Important differences from alpine-skiing injury patterns include higher rates of ankle and wrist injuries, a lower but still common knee injury rate, and a lower prevalence of thumb injury. We agree with the conclusions of others that nonrelease bindings and soft boots have contributed to the higher incidence of ankle injuries,[1,3,6-8] but we remain cautious in recommending hard-shelled boots with or without releasable bindings because they may simply shift the incidence of lower extremity injuries from the ankles to the knees, as has been observed in the evolution of alpine skiing. To reduce the incidence of wrist fractures and sprains, the use of wrist guards has been recommended in the sports of skateboarding, roller skating, and in-line skating.[17-19] Gloves with similar wrist support are now available for snowboarders and may prove beneficial in reducing wrist injuries, particularly in beginners. As with many sports, it is recommended that beginners seek professional instruction to learn proper techniques and safety precautions that may reduce their risk of injury. Chairlift loading and unloading practices must be reexamined.

REFERENCES

1. Shealy JE, Sundman PD: Snowboarding injuries on alpine slopes, *In* Johnson RJ, Mote CD Jr, Binet MH (Eds): Skiing Trauma and Safety: Seventh International Symposium. Philadelphia, Pa, American Society for Testing and Materials, 1989, pp 75-81

2. Aitkens M: Have snowboard, will soar. Physician Sports Med 1990; 18:114-120

3. Pino EC, Colville MR: Snowboard injuries. Am J Sports Med 1989; 17:778-781

4. Bladin C, Giddings P, Robinson M: Australian snowboard injury database study: A four-year prospective study. Am J Sports Med 1993; 21:701-704

5. Johnson RJ, Ettlinger CF, Campbell RJ, Pope MH: Trends in skiing injuries—Analysis of a 6-year study (1972-1978). Am J Sports Med 1980; 8:106-113

6. Johnson RJ: Skiing and snowboarding injuries: When schussing is a pain. Postgrad Med 1990; 83:36-38

7. Ganong RB, Heneveld EH, Beranek SR, et al: Snowboarding injuries: A report on 415 patients. Physician Sports Med 1992; 20:114-122

8. Abu-Laban RB: Snowboarding injuries: An analysis and comparison with alpine skiing injuries. Can Med Assoc J 1991; 145:1097-1103

9. Fujioka K, Panes P: Snowboarding injuries. Sports Med Dig 1989; 11:1-2

10. Glantz SA: Primer of Biostatistics, 3rd edition. New York, NY, McGraw-Hill, 1992

11. Ekeland A, Holtmoen A, Lystad H: Lower extremity equipment-related injuries in alpine recreational skiers. Am J Sports Med 1993; 21:201-205

12. Johnson RJ, Ettlinger CF: Alpine ski injuries: Changes through the years. Clin Sports Med 1982; 1:181-197

13. Newland CC: Gamekeeper's thumb. Orthop Clin North Am 1992; 23:41-48

14. Morgan JV, Davis PH: Upper extremity injuries in skiing. Clin Sports Med 1982; 1:295-308

15. Primiano GA: Skiers' thumb injuries associated with flared ski pole handles. Am J Sports Med 1985; 13:425-427

16. Van Dommelen BA, Zvirbulis RA: Upper extremity injuries in snow skiers. Am J Sports Med 1989; 17:751-753

17. Callé SC, Eaton RG: Wheels-in-line roller skating injuries. J Trauma 1993; 35:946-951

18. Banas MP, Dalldorf PG, Marquardt JD: Skateboard and in-line skate fractures: A report of one summer's experience. J Orthop Trauma 1992; 6:301-305

19. Lohmann M, Petersen AO, Pedersen OD: [Skateboard and rollerskate accidents]. Ugeskr Laeger 1990; 152:1591-1593 [Engl Abstr]

Conferences and Reviews

Applying the Results of Large Clinical Trials in the Management of Acute Myocardial Infarction

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Mortality from acute myocardial infarction has declined in recent years, largely due to the widespread application of new pharmacologic and mechanical interventions that have been tested in large, prospective, randomized clinical trials. For practicing generalists, we review the key data from such trials that have shaped the current management of patients with acute myocardial infarction. We discuss the roles of thrombolytic therapy, coronary angioplasty, nitrates, β- and calcium channel blockers, angiotensin-converting-enzyme inhibitors, magnesium, and antiarrhythmic and antithrombotic agents. In addition, we highlight critical unanswered questions in the management of this disorder.

(Sweeney JP, Schwartz GG: Applying the results of large clinical trials in the management of acute myocardial infarction. West J Med 1996; 164:238-248)

Coronary heart disease accounts for 700,000 deaths per year in the United States, with acute myocardial infarction (MI) accounting for about a third of these fatal events.[1,2] This article is intended for practicing physicians. We distill the results of the large, randomized clinical trials that have shaped the current optimal management of patients with acute MI, focusing on interventions that ordinarily would be implemented during the initial hospital admission for this disorder. The randomized trials discussed here have demonstrated that pharmacologic and mechanical interventions can reduce the morbidity and mortality from myocardial infarction if employed in appropriate patients.

Treating physicians, however, must never lose sight of three basic therapeutic goals in coronary care: relieving symptoms of ischemic pain or heart failure; assessing and optimizing hemodynamics; and assessing and treating serious rhythm disturbances. To review these fundamental principles of coronary care, readers are directed to a contemporary textbook of cardiology or internal medicine. The pursuit of these basic therapeutic goals may sometimes take precedence over the application of the results of the large clinical trials that are the focus of this review. Therapy must always be tailored to the individual patient, and it must be recognized that the general recommendations that follow may not apply to all patients with acute MI.

Thrombolytic Therapy

Acute MI results from prolonged ischemia, leading to myocardial necrosis. In most cases, this event is due to acute coronary artery thrombosis. Rare causes, including coronary artery spasm, systemic hypercoaguable states, and coronary artery dissection, are well recognized; these causes will not be the focus of the following discussion, however.

The primary event in the vast majority of acute MIs appears to be rupture of a lipid-rich coronary artery plaque. Once rupture occurs, underlying collagen and other subintimal substances are exposed, leading to platelet adhesion and aggregation and activation of the coagulation cascade. These events lead to acute coronary artery thrombosis and ischemia in the distribution of the affected vessel.[1,3,4] A classic angiographic study of Q-wave MI in 1980 identified thrombotic occlusion of an epicardial coronary artery as the proximate cause of acute MI in most infarctions.[5] This led to the development of both pharmacologic and mechanical strategies to reverse this thrombotic process, restore coronary perfusion, and possibly save myocardium at risk. Most of the effort has focused on the administration of thrombolytic drugs. The currently available agents include recombinant tissue plasminogen activator (t-PA), streptokinase, anistreplase (anisoylated plasminogen-streptokinase activator complex), and urokinase.

Placebo-controlled studies in the mid-1980s clearly showed that intravenous (IV) thrombolytic therapy results in improved survival. Although some of the benefit of coronary thrombolysis is likely due to the salvage of jeopardized myocardium, resulting in better left ventricular function, the substantial improvement in survival with thrombolytic therapy is disproportionate to the

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
CABG = coronary artery bypass grafting
GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico
GISSI-2, -3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [trial]
INR = international normalized ratio
ISIS-2, -3, -4 = Second, Third, and Fourth International Study of Infarct Survival
IV = intravenous
LIMIT-2 = Second Leicester Intravenous Magnesium Intervention Trial
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RESCUE = Randomized Evaluation of Salvage Angioplasty With Combined Utilization of Endpoints
SWIFT = Should We Intervene Following Thrombolysis? [trial]
TIMI II, IIIB = Thrombolysis in Myocardial Infarction [trials] phase II, IIIB
t-PA = tissue plasminogen activator

modest improvement in left ventricular function. It appears that benefit may be derived from a patent infarct-related coronary artery, independent of myocardial salvage.[6] Overall, the use of IV thrombolytic agents within about six hours of the onset of symptoms of acute MI results in a 25% to 30% reduction in mortality, from about 10% to about 7% (Figure 1).[1,7]

Which Patients Should Receive Thrombolytic Agents?

The generally accepted indications and contraindications for thrombolytic therapy are shown in Tables 1 and 2, respectively. Patients presenting with ST-segment elevation in the anterior leads within six hours of the onset of pain clearly benefit from thrombolytic therapy, with reductions of both in-hospital and late mortality. A trend toward a reduction in mortality has been noted in patients with inferior-wall MI (ST-segment elevation in leads II, III, and aVF); a statistically significant reduction in mortality has not been demonstrated, however.[7] Nonetheless, it is reasonable to administer a thrombolytic agent in patients with inferior-wall infarction, especially in cases

TABLE 1.—Characteristics of Candidates for Thrombolysis

Characteristic	Candidates: Optimal*	Candidates: Acceptable†
Symptom duration, hr	<6	Between 6 and 24
Location of MI by ECG	Anterior wall	Nonanterior wall
Contraindications‡	No absolute or relative contraindications	Relative contraindication(s) only

ECG = electrocardiogram, MI = myocardial infarction

*An optimal candidate would possess all of the characteristics listed in the left column.
†An acceptable candidate may possess one or more characteristics listed in the right column.
‡See Table 2.

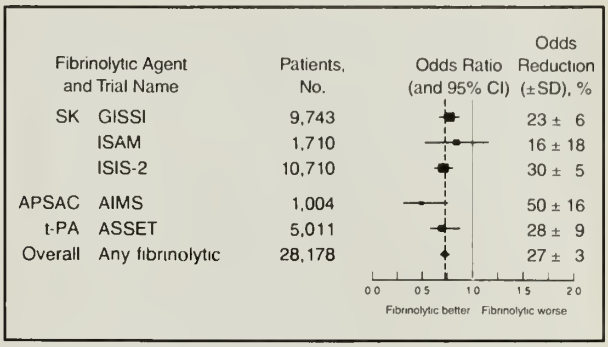

Figure 1.—Mortality reduction is shown in large, placebo-controlled trials of intravenous thrombolytic therapy for acute myocardial infarction. Overall (pooled) data indicate a 27% ± 3% reduction in mortality with thrombolytic therapy (from Reeder and Gersh[1]). AIMS = APSAC Intervention Mortality Study, APSAC = anistreplase (anisoylated plasminogen-streptokinase activator complex), ASSET = Anglo-Scandinavian Study of Early Thrombolysis, CI = confidence interval, GISSI = Gruppo Italiano per lo Studio della Strepochinasi nell'Infarto Miocardico, ISAM = Intravenous Streptokinase in Acute Myocardial infarction, ISIS-2 = 2nd International Study of Infarct Survival, SD = standard deviation, SK = streptokinase, t-PA = tissue plasminogen activator

suggesting a more complex infarction—that is, those with hemodynamic compromise, right ventricular involvement, or widespread electrocardiographic changes—with a low to moderate risk of bleeding. Patients presenting with new left bundle branch block and a clinical history consistent with acute MI also appear to benefit from thrombolytic therapy.[7] Several studies have investigated whether patients presenting with new ischemic ST-segment depression—that is, clinical syndromes of unstable angina or non–Q-wave MI—benefit from thrombolytic therapy. Despite the fact that many of these patients have angiographic evidence of coronary thrombi, neither the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), the Second International Study of Infarct Survival (ISIS-2), nor the Thrombolysis in Myocardial Infarction phase IIIB (TIMI IIIB) trial demonstrated a survival benefit from thrombolytic therapy in such patients.[8-10]

Elderly patients are at a higher risk for bleeding, particularly intracranial bleeding, as a complication of thrombolytic therapy. This has led to reluctance on the part of some clinicians to administer these agents to these patients. Data from the Fibrinolytic Therapy Trialists' Collaborative Group, which pooled results from several major trials, demonstrated that there are larger proportional reductions in mortality among younger patients than among elderly patients.[7] The absolute reduction in mortality with thrombolytic therapy may actually be greater in elderly patients, however: Data from the ISIS-2 study revealed that combined streptokinase and aspirin use markedly reduced mortality from 23.8% to 15.8% in patients older than 70 years, compared with a reduction in mortality from 10.6% to 6.1% in patients younger than 70 years (Figure 2).[9,11] Therefore, no arbitrary upper age limit should be

TABLE 2.—Contraindications to Thrombolytic Therapy

Controindication	*Example*
Absolute	Active bleeding
	Known intracranial tumor
	Stroke within 6 mo
	Major surgical procedure, gastrointestinal hemorrhage, or major trauma within 6 wk
	Head trauma within 1 mo
	Any clinical evidence of acute aortic dissection
	Bleeding diathesis or chronic liver disease with portal hypertension
Relative	History of recent gastrointestinal bleeding or active peptic ulcer
	Cardiogenic shock—consider emergent PTCA instead
	Uncontrolled hypertension—≥165/95 mm of mercury
	Prolonged or traumatic cardiopulmonary resuscitation
	Remote history of cerebrovascular disease
	Proliferative diabetic retinopathy

PTCA = percutaneous transluminal coronary angioplasty

imposed for thrombolytic therapy for acute MI. Rather, thrombolytic therapy should be considered for any patient, regardless of age, after a careful evaluation for indications and contraindications.

Hypertension increases the risk of intracranial hemorrhage as a complication of thrombolytic therapy. Hypertension at the time of thrombolytic drug administration—defined in one study as a systolic blood pressure ≥165 mm of mercury, diastolic blood pressure ≥95 mm of mercury, or both[12]—is a stronger risk factor for cerebral hemorrhage than a previous history of hypertension. Every attempt should be made to reduce the blood pressure below these limits before administering a thrombolytic drug. Patients with a history of hypertension are also at increased risk for aortic dissection, with signs and symptoms that may mimic those of acute MI. Clinical evidence suggesting aortic dissection is an absolute contraindication to thrombolytic therapy.

Timing of Thrombolytic Therapy

Perhaps the most important consideration in the use of a thrombolytic agent is that the time from the onset of symptoms to the administration of the drug bears a strong, inverse relationship to the ensuing reduction in mortality. Efficacy is clearly and sharply decremental over the first few hours after symptoms start. The improved survival from treatment with thrombolytic agents is related in part to myocardial salvage—that is, a reduction in the ratio of ultimately infarcted to initially jeopardized myocardium. The time dependence of myocardial salvage has been demonstrated in studies of dogs that showed that infarction is essentially complete within four to six hours of coronary artery occlusion.[6] Data from the ISIS-2 trial, however, revealed a survival benefit from aspirin and streptokinase use that persisted through 24 hours after the onset of symptoms.[9] In addition, results from the Late Assessment of Thrombolytic Efficacy (LATE) trial revealed a survival benefit from t-PA use in patients treated 6 to 12 hours from the onset of pain.[13] The mechanisms for the benefit of late reperfusion may include the prevention of necrosis in infarct border zones, improved electrical stability of reperfused myocardium, and attenuation of postinfarction ventricular enlargement.[6] Thus, it appears that administering a thrombolytic agent 6 to 12 hours (and perhaps as long as 24 hours) from the start of pain confers a survival benefit, albeit reduced from earlier reperfusion. It must be reemphasized that because the benefit of thrombolytic therapy is decremental with the passage of time, it is imperative that treating physicians pursue an early and accurate diagnosis of acute MI to achieve the maximal benefit of thrombolytic therapy. In fact, a recent European report indicates that prehospital thrombolytic therapy, administered by emergency medical personnel, reduces cardiac mortality compared with treatment after arrival at a hospital (median treatment time, 55 minutes later).[14]

Which Thrombolytic Agent Should Be Administered?

Three trials—ISIS-3,[15] GISSI-2 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico),[16]

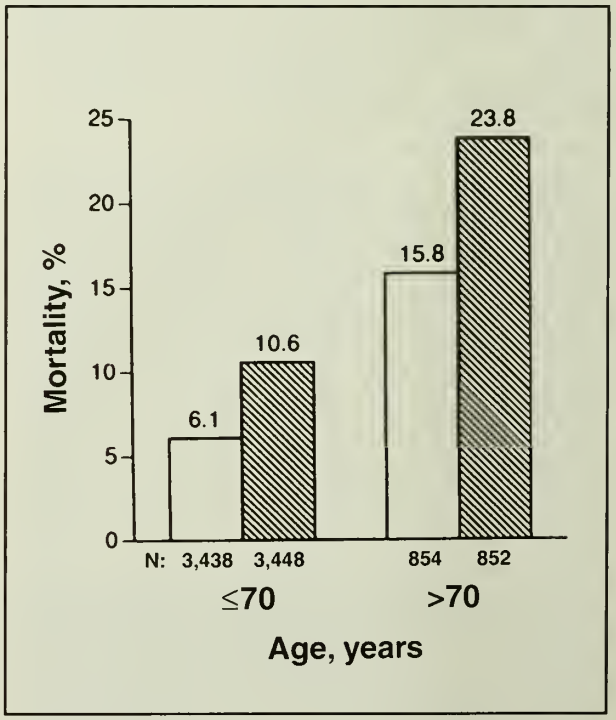

Figure 2.—The graph shows the mortality from acute myocardial infarction in the 2nd International Study of Infarct Survival, dichotomized by age 70 or younger or older than 70 years. The white bars represent patients who received streptokinase and aspirin, and the shaded bars represent the group receiving placebo. Although older patients have higher mortality, with or without thrombolytic therapy, they achieve a greater absolute reduction in mortality with thrombolytic therapy (from Muller and Topol[11]).

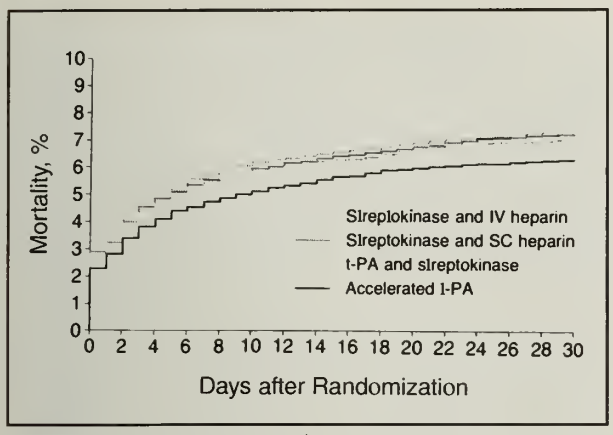

Figure 3.—The graph shows the 30-day mortality in the 4 treatment groups of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. The group receiving accelerated tissue plasminogen activator (t-PA) had significantly lower mortality than any of the other treatment groups (from the GUSTO investigators[17]). IV = intravenous, SC = subcutaneous

and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)[17]—have compared the efficacy of streptokinase, anistreplase, and t-PA as well as different anticoagulation regimens in tens of thousands of patients. Neither GISSI-2 nor ISIS-3 revealed a significant difference in mortality between the various agents, but the use of streptokinase showed a significantly lower incidence of stroke in the ISIS-3 trial. The lack of demonstrable benefit of t-PA use over that of streptokinase in ISIS-3 and GISSI-2 was questioned because both studies used delayed subcutaneous rather than immmediate IV heparin after administering a thrombolytic drug. In addition, pilot data suggested that the efficacy of t-PA could be enhanced by administering the drug over a shorter period of time. These concerns provided impetus for the GUSTO trial, which randomly assigned 41,121 patients to one of four treatment groups: streptokinase with the immediate administration of IV heparin, streptokinase followed in four hours by subcutaneous heparin, accelerated t-PA—t-PA administered over 90 minutes with most of the dose given in the first 30 minutes, instead of the usual 3-hour infusion—followed by immediate IV heparin, or combined t-PA and streptokinase with IV heparin. Each group received aspirin and a β-blocker whenever possible. The accelerated t-PA regimen resulted in a 1% lower overall mortality than any of the other regimens, a difference that was significant (Figure 3). The mortality benefit came at the expense of a slight excess of hemorrhagic strokes with t-PA use compared with the streptokinase regimens. Nonetheless, the incidence of a combined end point of death or disabling stroke was lower with the accelerated t-PA regimen than with the streptokinase regimens. When subgroup analysis was done, the incremental benefit of t-PA use over that of streptokinase was greatest in patients younger than 75 years of age, with anterior MI, or presenting early after symptoms began (Figure 4). The explanation for the first subgroup effect is that the greater propensity for stroke in elderly patients with thrombolytic treatment was amplified by the use of t-PA. The explanation for the benefit of the use of t-PA over that of streptokinase in patients with anterior wall or early infarcts (or both) is most likely that these are the subsets most likely to benefit from thrombolysis in general, therefore affording greater statistical power to detect a difference between drugs.

Other considerations may enter into the decision to use t-PA. Because t-PA is less likely to decrease the blood pressure than streptokinase, the use of the former may be preferable in patients with borderline hypotension. Because streptokinase and anistreplase are antigenic, a blunted therapeutic response or allergic reaction may occur in patients who have previously received either drug. Such patients should also receive t-PA for coronary thrombolysis. Whereas t-PA is considerably more costly than streptokinase, the incremental cost per year of life saved (based on GUSTO results) compares favorably with other interventions employed in standard medical practice.[18]

In summary, the use of t-PA appears to afford a modest but statistically significant mortality benefit over that of streptokinase when given in an accelerated-dose regimen and followed by IV heparin. Patients older than 75 years, however, do not achieve this benefit because of an increased risk of stroke. Therefore, in most cases, eligible patients older than 75 years should be treated with streptokinase. In patients who receive streptokinase, there is no convincing evidence of a benefit from full-dose IV heparin over subcutaneous heparin. In patients with hypotension or recent exposure to streptokinase, it may be prudent to use t-PA, even in elderly patients.

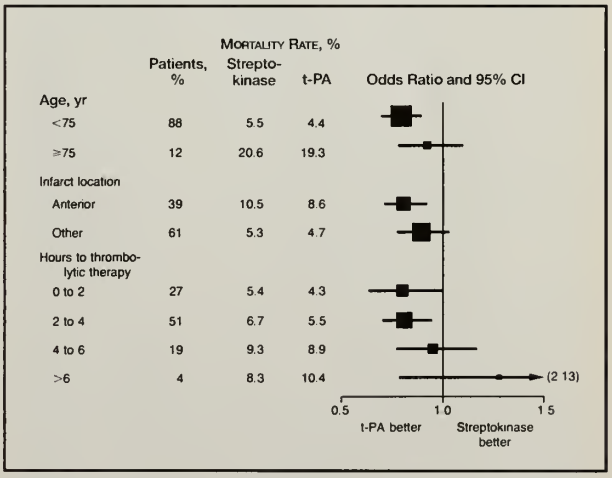

Figure 4.—Subgroup analysis is shown of mortality in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. The subgroups showing the greatest incremental benefit of accelerated tissue plasminogen activator (t-PA) over streptokinase regimens were younger than 75 years, had an anterior wall infarct, and were patients in whom thrombolytic therapy was started earlier (from the GUSTO investigators[17]). CI = confidence interval

TABLE 3.—Indications for Coronary Angioplasty in Acute Myocardial Infarction

Coronary Angioplasty	Indication for Use
Primary	As an alternative to thrombolytic therapy
Primary	In patients with contraindications to thrombolytic therapy or in patients unlikely to benefit from thrombolysis—for example, those with cardiogenic shock
Rescue	In patients who have received thrombolytic therapy that is suspected or proved to have failed
Adjunctive	In patients initially treated with thrombolysis who subsequently show either spontaneous or easily inducible ischemia

Percutaneous Transluminal Coronary Angioplasty

As described earlier, the focus of current therapy for acute MI is reperfusion of the infarct-related artery. With increasing awareness of the limitations of thrombolytic agents—for example, contraindications to their use, complications related to bleeding, and failure to restore perfusion in as many as a third of cases—the role of percutaneous transluminal coronary angioplasty (PTCA) is becoming better defined. Table 3 lists four situations in which PTCA may be useful in patients with acute MI.

Initially, several small series of consecutive patients demonstrated the feasibility and efficacy of primary angioplasty for acute MI.[19] Subsequently, several randomized trials compared the use of primary PTCA with thrombolytic therapy.[20-22] In these trials, PTCA was accomplished in an average time of less than 60 minutes from hospital presentation. In the Primary Angioplasty in Myocardial Infarction (PAMI) trial,[20] 395 patients were randomly assigned to receive primary PTCA versus t-PA. The combined incidence of death and nonfatal reinfarction was lower in the group receiving PTCA. In addition, no strokes occurred in the PTCA group, versus seven cases in the t-PA group. In a randomized trial from the Netherlands comparing the use of streptokinase with that of primary PTCA, the principal end points of recurrent ischemia, ejection fraction, and coronary patency all favored the use of primary PTCA.[21] There were no significant differences in death or stroke rates, however. Results from a Mayo Clinic (Rochester, Minnesota) study revealed no significant difference between the use of primary PTCA or t-PA in left ventricular function or mortality,[22] but patients in the PTCA group had briefer hospital stays, fewer readmissions within six months, and lower six months' follow-up cost. Thus, in institutions offering prompt access to a cardiac catheterization laboratory with highly experienced operators, primary PTCA is a reasonable alternative and perhaps even a superior therapeutic strategy to thrombolysis. The greatest use of PTCA, however, is in a patient with a contraindication to thrombolysis who would otherwise be precluded from achieving reperfusion.

The concept of rescue angioplasty emerged with the increasing recognition that thrombolytic therapy achieved patency rates of only 60% to 80%. The Randomized Evaluation of Salvage Angioplasty With Combined Utilization of Endpoints (RESCUE) trial enrolled patients who had an occluded infarct-related artery demonstrated by coronary angiography despite treatment with a thrombolytic agent and who had an onset of chest pain within eight hours of enrollment.[23] Subjects were randomly selected to receive either conservative therapy (aspirin, heparin, and coronary vasodilators) or conservative therapy plus PTCA. In 92% of patients with occluded vessels, PTCA was successful, and the incidence of the combined end point of death or severe heart failure was substantially reduced in this group. The major obstacle to the strategy of rescue angioplasty, however, has been to identify patients in whom thrombolysis has failed without doing early coronary angiography in every case. This problem arises because the clinical markers of thrombolytic failure—persistent pain, persistent ST-segment elevation, the absence of reperfusion arrhythmias—have only modest predictive value. Thus, the successful application of rescue angioplasty in clinical practice may be impeded because clinicians hoping to achieve the beneficial outcome noted in the RESCUE trial would have to submit many patients to emergent coronary angiography to identify a subset with failed thrombolysis.

The role of deferred adjunctive PTCA following thrombolytic therapy was addressed by two large trials, phase II of the Thrombolysis in Myocardial Infarction study (TIMI II) and the Should We Intervene Following Thrombolysis? (SWIFT) trial.[24,25] In the TIMI II trial, an invasive strategy of angiography and PTCA attempted early (18 to 48 hours after thrombolysis) was compared with a conservative strategy in which angiography and PTCA were performed only if there was recurrent spontaneous ischemia or ischemia noted on predischarge exercise testing. Of the patients in the invasive arm, 57% underwent PTCA compared with 13% in the conservative arm. There was no significant difference between groups in the incidence of death, reinfarction, or left ventricular function at either six weeks or one year of follow-up. The results of the SWIFT trial were similar. Thus, angiography and PTCA need not be done on every patient after thrombolysis. The use of deferred PTCA should be reserved for patients with a complicated clinical course or those who continue to have spontaneous or easily induced ischemia.

The final indication for PTCA appears to be in treating patients with acute MI and cardiogenic shock. In the first GISSI trial, administering streptokinase appeared to be of no benefit over placebo in patients with acute MI and cardiogenic shock.[8] The mortality rates in both groups were dismal, at about 70%. Several investigators have reported survival to be markedly improved in patients with shock successfully treated with primary PTCA.[26] Thus, in patients presenting with acute MI and cardiogenic shock, the use of emergent PTCA should be pursued if logistically possible.

Coronary Artery Bypass Graft Surgery

There are no large, randomized clinical trials comparing the use of early coronary artery bypass grafting (CABG) with that of PTCA or thrombolytic therapy in the management of acute MI. Early CABG—within 24 hours of the onset of symptoms—can be done in selected patients with in-hospital mortality as low as 6%.[27] Similarly, nonemergent CABG can be performed in the days and weeks following acute MI without an increase in mortality.[28]

Because the strongest predictors of an adverse prognosis after acute MI are the extent of left ventricular dysfunction and recurrent ischemia (spontaneous or inducible), patients with one or both of these characteristics are most likely to benefit from early revascularization. When such patients are found to have left main or multivessel coronary artery disease or coronary lesions not readily amenable to PTCA, CABG may be the most appropriate revascularization strategy. Other possible indications for doing early CABG in patients with acute MI include failed thrombolysis, contraindications to thrombolysis, cardiogenic shock, or mechanical complications of acute MI such as acute ventricular septal defect or severe mitral regurgitation.

Adjunctive Pharmacologic Therapy

Nitrates

Several studies have investigated whether the routine use of nitrates reduces morbidity and mortality from acute MI. In a study before the development of thrombolytic therapy for acute MI, it was reported that administering IV nitroglycerin limited infarct size, reduced the incidence of cardiogenic shock and mural thrombus formation, and limited infarct expansion.[29] In addition, there was a significant reduction in mortality in treated patients. In a meta-analysis of trials of IV nitroglycerin therapy in acute MI conducted before the availability of thrombolytic therapy, there was a remarkable 35% to 40% reduction in mortality in treated patients.[30]

More recently, two large trials that investigated the effect of nitrates in conjunction with thrombolytic therapy have dampened the enthusiasm for the routine use of these agents. The GISSI-3 trial randomly assigned more than 19,000 patients either to receive IV nitroglycerin (on the first hospital day) followed by transdermal nitroglycerin or to an open control group.[31] Six-week mortality was not statistically different between the two groups. The Fourth International Study of Infarct Survival (ISIS-4[32]) randomly assigned 58,000 patients to receive controlled-release oral nitrate versus placebo. Again, there was no significant difference in mortality between the groups.

In conclusion, nitrates should be used whenever indicated to treat ongoing ischemia, ischemic pain, or pulmonary congestion. Recent data, however, do not support their routine use beyond these indications.

β-Blockers

The use of β-blockers in patients with acute MI was prompted by studies in animals that suggested that these agents might reduce infarct size, exert an antiarrhythmic effect, and prevent cardiac rupture. Acute β-blockade is clearly useful in subsets of patients with acute MI and ongoing ischemia or hyperdynamic circulation. Studies of the routine early administration of IV β-blockers in acute MI have been less convincing, however. In the Metoprolol in Acute Myocardial Infarction (MIAMI) trial,[33] the administration of IV metoprolol tartrate reduced early mortality by 13%, a result that was not statistically significant. In a study of 8,000 patients, the ISIS-1 showed a borderline-significant 15% reduction in one-week mortality using IV atenolol.[34] Both of these trials were conducted before the development of thrombolytic therapy. The use of early IV β-blockade in conjunction with thrombolytic therapy was investigated in the TIMI II trial.[24] Following thrombolysis with t-PA, patients were randomly assigned to receive either immediate IV metoprolol followed by oral metoprolol therapy or delayed oral metoprolol therapy beginning on day 6. The group receiving early IV metoprolol showed small reductions in the rates of reinfarction and recurrent ischemia during the initial six days of treatment; there was no significant difference in six-day mortality or in any end point at six weeks' follow-up. Thus, IV β-blockade during the acute phase may be marginally effective in reducing short-term recurrent ischemic events, and perhaps early mortality, after acute MI.

In contrast, the use of long-term oral β-blockade after myocardial infarction is a proven and powerful therapeutic intervention. Before the availability of thrombolytic therapy, several large randomized trials demonstrated 20% to 30% reductions in mortality with β-blockade at two to three years' follow-up (Figure 5).[3,35-37] Much of this benefit appears to be related to a reduced incidence of sudden death. Concern by some physicians about using β-blockers in patients with depressed left ventricular function has limited their application in this patient population. But closer examination of trials of β-blockade following acute MI reveals that patients with depressed left ventricular function actually have the greatest survival benefit from such therapy.[38,39]

There are unanswered questions regarding the long-term efficacy of β-blockade in patients who also receive thrombolysis, CABG, or PTCA. The efficacy of β-blockers when used with other classes of drugs such as angiotensin-converting-enzyme (ACE) inhibitors or antiarrhythmic agents is also uncertain. We think, however, that the striking mortality benefit documented in trials before thrombolytic therapy was available warrants the use of long-term β-blockade following myocardial infarction whenever possible.

Angiotensin-Converting-Enzyme Inhibitors

Recent work in both animals and humans has shown that infarct expansion and left ventricular remodeling

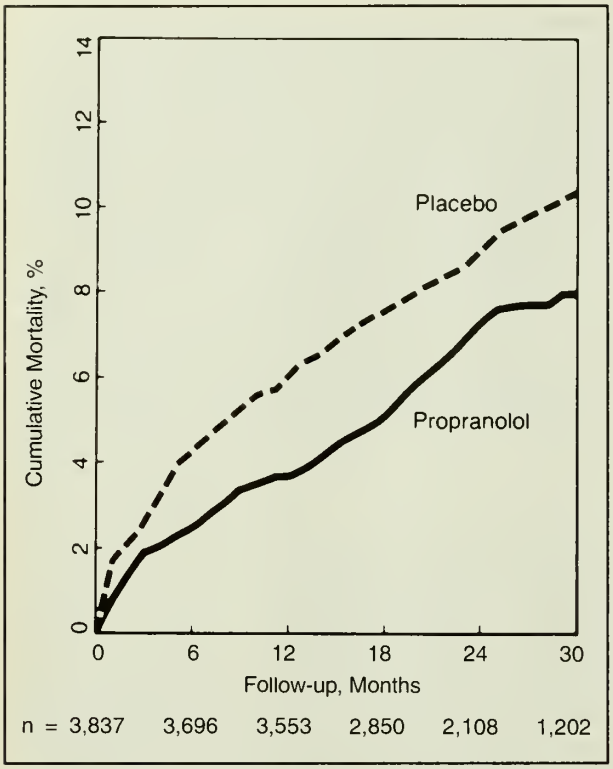

Figure 5.—Mortality data from the β-Blocker Heart Attack Trial (BHAT) shows that long-term propranolol therapy significantly reduced mortality after myocardial infarction (from the BHAT Research Group[35]). n = number of patients observed through each time point.

contribute to the late detrimental effects of acute MI and that administering ACE inhibitors can attenuate these processes.

The Survival and Ventricular Enlargement trial[40] randomly assigned 2,230 patients to receive either captopril or placebo starting 3 to 16 days after myocardial infarction. All patients had an ejection fraction of less than 40%, but none had symptomatic congestive heart failure. The administration of captopril reduced the rates of death, congestive heart failure, and recurrent acute MI by about 20% over a mean follow-up period of 42 months (Figure 6). Of note is that relatively high doses of captopril were used, with a target dose of 50 mg three times a day. Subgroup analysis indicated that the benefit from captopril use was independent of age, sex, or treatment with β-blocking or thrombolytic agents.

The Survival and Ventricular Enlargement trial raised the question of whether ACE inhibitors should be used after acute MI, regardless of the severity of left ventricular dysfunction. The GISSI-3 and ISIS-4 are large trials that investigated such generalized use of early oral ACE inhibitors. The GISSI-3 trial randomly assigned patients within 24 hours of acute MI and with a systolic blood pressure of more than 100 mm of mercury either to receive lisinopril or to an open control group.[31] At six weeks, active treatment resulted in an 11% decrease in mortality compared with the control group (0.8% absolute mortality difference). Of note, only 5% of these patients had an ejection fraction of 35% or less. The ISIS-4 trial, which randomly assigned patients to receive either placebo or captopril therapy within 24 hours of an acute MI, demonstrated a 9% reduction in mortality at four weeks.[32] Other studies have shown mortality benefits from the use of ramipril and zofenopril after acute MI.[41,42] Therefore, the salutary effect of ACE inhibitors is most likely a class effect and not limited to any individual compound.

Thus, ACE inhibitor treatment reduces mortality after acute MI, with the greatest benefit in patients with substantial left ventricular dysfunction. Because available data indicate a beneficial effect of ACE inhibitor therapy in patients treated concurrently with β-blockers,[40] our practice is to use both classes of drug whenever possible after acute MI.

Calcium Channel Antagonists

Although calcium channel blockers such as nifedipine, verapamil, and diltiazem provide a valuable therapeutic option in patients with ongoing angina, hypertension, or supraventricular tachycardia, studies investigating their routine use after acute MI have dimmed early expectations.

The trials assessing treatment with nifedipine in patients with acute MI have used several end points, including infarct size, reinfarction, and mortality.[43] The studies are problematic because several of them enrolled patients with unstable angina. Nifedipine appears to provide no benefit in terms of infarct size or rate of reinfarction. None of the trials has shown a reduction in either acute or long-term mortality. In fact, some trials

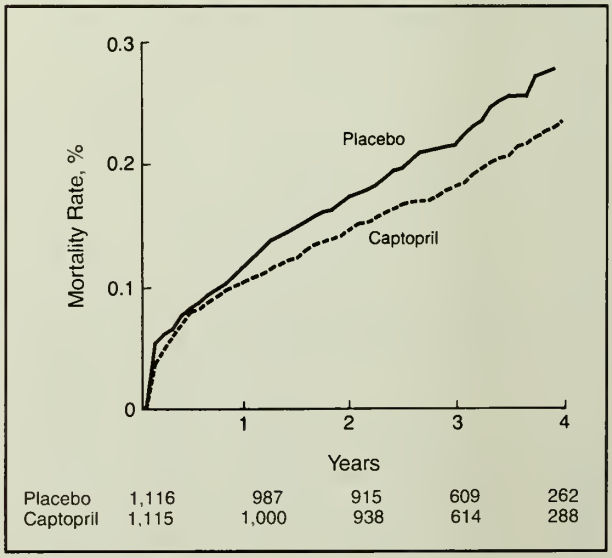

Figure 6.—Data from the Survival and Ventricular Enlargement trial shows a 19% risk reduction in long-term mortality with captopril therapy after myocardial infarction in patients with a left ventricular ejection fraction of less than 40% ($P = .02$). The number of patients observed at each time point is indicated at the bottom of the graph (from Pfeffer et al[40]).

have indicated a slight trend in the opposite direction. Thus, the use of nifedipine in myocardial infarction cannot be recommended.

The first Danish Verapamil Infarction Trial (DAVIT-I) randomly assigned 1,436 patients with acute MI to receive placebo or an IV bolus of verapamil followed by oral verapamil.[44] The study showed no significant difference in mortality or reinfarction at six months. The second Danish Verapamil Infarction Trial (DAVIT-II) randomly assigned more than 1,600 patients to receive placebo versus verapamil therapy, begun in the second week after acute MI.[45] At a mean follow-up of 16 months, there was no significant difference in mortality, but verapamil treatment significantly reduced the combined incidence of death or reinfarction. The effect appeared to be greatest in patients without heart failure.

Two trials have assessed the effects of diltiazem use in patients with acute MI. In the Diltiazem Reinfarction Study of non–Q-wave infarctions, treatment with diltiazem was initiated 24 to 72 hours after acute MI and continued for as long as 14 days.[46] Diltiazem use reduced the rate of early reinfarction by 51% and the frequency of severe angina by 49%. There was no significant effect on mortality, however. In the Multicenter Diltiazem Postinfarction Trial, 2,466 patients were randomly assigned to receive diltiazem or placebo within 3 to 15 days after acute MI.[47] Total mortality rates were nearly identical in the two treatment groups. A subgroup analysis revealed that in patients without radiographic pulmonary congestion, diltiazem use reduced the incidence of cardiac events (death or nonfatal infarction). In those patients with radiographic pulmonary congestion, diltiazem therapy was associated with an increase in the number of cardiac events. A similar effect was noted with respect to the ejection fraction, which was dichotomized at 40%.

Thus, the routine use of calcium channel antagonists cannot be justified in patients with acute MI on the basis of available data. The use of diltiazem or verapamil may be of benefit in patients with well-preserved left ventricular function, but these patients compose a group whose prognosis is good regardless of adjunctive drug therapy.

Magnesium Sulfate

The use of magnesium sulfate has several possible benefits in acute MI. In experimental models, it acts to dilate coronary vessels, stabilize cell membranes, decrease platelet aggregation, and reduce infarct size. Magnesium opposes calcium entry into cells, which has been implicated in reperfusion injury.[48] In addition, magnesium is inexpensive and safe to administer.

A meta-analysis of six trials of magnesium sulfate use in patients with acute MI revealed about a 50% reduction in mortality.[49] These data prompted the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), which randomly assigned 2,300 patients to receive placebo versus IV magnesium sulfate, administered at a median of three hours after the onset of chest pain and continued for 24 hours.[50] The 28-day mortality was reduced by 24%, and the incidence of left ventricular failure was reduced by 25% in the magnesium-treated patients, results that achieved borderline significance. Subgroup analysis indicated that the benefit of magnesium use was independent of treatment with thrombolytic agents, aspirin, β-blockers, or calcium channel blockers. The promising results of LIMIT-2 prompted further investigation of the possible role of magnesium sulfate in the much larger ISIS-4 trial. In 58,000 patients,[32] administering IV magnesium sulfate did not appear to confer any mortality benefit compared with the open control group. The reason for the differences in the results of these two studies is unclear. The dose of magnesium was nearly identical. An intriguing hypothesis is that early administration of magnesium is required to achieve a therapeutic benefit. The median time to administration was three hours in LIMIT-2, but eight hours in the ISIS-4 trial. In animal models, the beneficial effects of magnesium therapy have been greatest when it is given before reperfusion, perhaps reducing reperfusion injury. Thus, it is possible that in ISIS-4, magnesium was administered too late to have a beneficial effect.

Thus, the therapeutic role of magnesium sulfate in acute MI remains in question. The drug can be administered safely to patients who do not have hypotension, renal failure, bradycardia, or heart block. Current data, however, make its use reasonable only in patients without contraindications in whom treatment can be initiated soon after the onset of symptoms.

Antiarrhythmic Agents

Prophylactic Lidocaine Hydrochloride

Lidocaine hydrochloride is effective in preventing primary ventricular tachycardia or fibrillation during the initial 24 to 48 hours after acute MI. In the past, the prophylactic use of lidocaine was recommended for patients with acute MI, regardless of the occurrence of "warning arrhythmias"—multifocal, frequent, or early premature ventricular contractions or nonsustained ventricular tachycardia. The results of a randomized trial and a meta-analysis of several smaller trials suggest that this strategy does not improve mortality and, in fact, may increase mortality during the treatment period.[51,52] Thus, the strategy of using prophylactic lidocaine in all patients with acute MI cannot be recommended.

Chronic Suppressive Antiarrhythmic Therapy

A substantial portion of the mortality following acute MI is the result of sudden cardiac death, presumably as a consequence of ventricular arrhythmias. Furthermore, frequent ventricular ectopy after acute MI has been identified as a risk factor for sudden death. Therefore, the attempted suppression of ventricular ectopy was a logical strategy to reduce mortality after acute MI. Unfortunately, the results of the Cardiac Arrhythmia Suppression Trial failed to support this concept.[53] In this trial, patients who had sustained an acute MI six days to two years before enrollment and had more than six

premature ventricular contractions per hour but no ventricular tachycardia episode longer than 15 consecutive beats were randomly assigned to receive either placebo or a type Ic antiarrhythmic agent (flecainide, encainide, or moricizine). An unexpected, significant increase in the incidence of sudden death and total mortality was found in the treated group. This adverse outcome was thought to be due to the drugs' proarrhythmic properties. Thus, the use of type Ic agents should be avoided in patients who have had acute MI, and any antiarrhythmic agent should be subjected to the careful scrutiny of large randomized, prospective trials before its use can be routinely recommended in these patients.

Amiodarone

Amiodarone is thought to have fewer proarrhythmic effects than conventional antiarrhythmic agents. Therefore, several trials have been undertaken to evaluate whether empiric amiodarone therapy can reduce mortality in patients who have had acute MI. Two small studies have been completed, and two larger trials are currently underway.

In a study in Poland, more than 600 patients who had had acute MI and who were ineligible to receive β-blockers (because of heart failure, diabetes mellitus, asthma, or peripheral vascular disease) were randomly assigned to receive either placebo or amiodarone (target dose, 400 mg per day) for a year.[54] Active treatment resulted in a borderline-significant reduction in cardiac mortality.

The Basel Antiarrhythmic Study of Infarct Size (BASIS) randomly assigned patients with complex ventricular arrhythmias after acute MI to one of three groups[55]: "individualized" antiarrhythmic therapy (quinidine, mexilitene, diisopyramide, flecainide, or sotalol, based on the results of Holter monitoring); low-dose empiric amiodarone, 200 mg per day; or open control. During the one-year follow-up, the mortality rates were 10% in the individualized therapy group, 5% in the amiodarone group, and 13% in the control group (Figure 7), representing a borderline-significant survival advantage for the amiodarone-treated patients.

These early small trials suggest that the use of amiodarone may improve survival in selected patients who have had acute MI. Several key questions remain unanswered, however. How does amiodarone therapy compare with the use of β-blockers in reducing mortality? Are there any additive benefits of the two classes of drugs? Which subgroups of patients derive the greatest benefit from amiodarone? Two larger trials in progress, the Canadian Amiodarone Myocardial Infarction Trial (CAMIAT) and the European Myocardial Infarction Amiodarone Trial (EMIAT), promise to shed light on these and other questions.

Aspirin and Oral Anticoagulants

Aspirin

The use of aspirin in acute MI was evaluated in the ISIS-2 trial.[9] In this study, 17,187 patients presenting

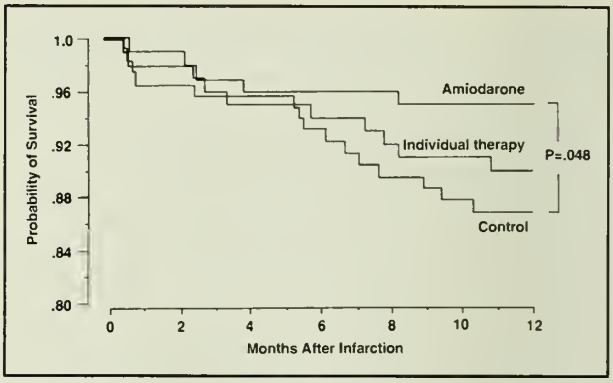

Figure 7.—Data from the Basel Antiarrhythmic Study of Infarct Size shows a borderline statistically significant ($P < .05$) improvement in survival with amiodarone therapy after myocardial infarction in patients with complex ventricular ectopy (from Burkart et al[55]).

within 24 hours of symptoms were randomly assigned to receive streptokinase, aspirin, both, or neither. Half of the initial aspirin dose was chewed for more rapid absorption. Mortality was reduced by 23% in the aspirin-only group, 25% in the streptokinase-only group, and 42% in the group receiving both aspirin and streptokinase. Thus, taking aspirin alone reduces the mortality from acute MI and appears to exert an additive effect when combined with streptokinase. Therefore, it is imperative that all patients receiving thrombolytic therapy be treated simultaneously with aspirin. In patients who are not candidates for thrombolysis, aspirin therapy should be initiated as soon as possible, whenever possible.

To date, six randomized, placebo-controlled trials of secondary prevention with aspirin have been conducted. Although the use of aspirin tended to reduce mortality, no significant benefit from therapy was shown in any single study, possibly because of inadequate statistical power. Pooling of data indicates that long-term aspirin therapy results in a 10% to 15% reduction in mortality and a 20% to 30% reduction in the incidence of reinfarction.[3,4] As a result, the use of aspirin is recommended for the secondary prevention of cardiovascular morbidity and mortality after acute MI.

Oral Anticoagulants

Warfarin sodium has been used to treat acute MI for more than 30 years. Until recently, however, there has been a dearth of well-controlled data supporting its use. The Warfarin Reinfarction Study (WARIS) was designed to assess the efficacy of warfarin use in reducing mortality and the incidence of reinfarction after acute MI.[56] Patients were randomly assigned at a mean of 27 days following acute MI to receive warfarin (target international normalized ratio [INR], 2.8 to 4.8) or placebo. An intention-to-treat analysis revealed a 24% reduction in mortality and a 34% reduction in the incidence of acute MI during a mean follow-up of 37 months (Figure 8). In addition, there was a 55% reduction in the incidence of stroke. This was achieved at the expense of a slightly higher incidence of major bleeding.

In the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial, patients were randomly assigned to receive an oral anticoagulant (INR 2.8 to 4.8) versus placebo.[57] More than 3,400 patients were randomly assigned within six weeks of discharge after acute MI and observed for a mean of 37 months. There was no significant difference in mortality or the incidence of recurrent acute MI or stroke as individual end points. Event-free survival—without death, acute MI, stroke, or bleeding—was significantly greater in the anticoagulant group, however.

Emboli from left ventricular mural thrombus due to acute MI account for 15,000 to 25,000 strokes each year. Mural thrombus formation is most likely to occur in patients with anterior MI with substantial regional wall motion abnormality, in whom the incidence may be as high as 30% to 40%.[58] The risk of suffering an event is greatest in the first ten days after the infarction, but persists for one to three months. A meta-analysis of anticoagulation trials suggests that the incidence of mural thrombus occurring after acute anterior MI can be reduced with these agents.[59] In addition, treatment with anticoagulants appears to reduce the rate of systemic embolization in patients with a known mural thrombus.

Although the administration of warfarin may reduce morbidity and mortality after acute MI, it is unclear whether its use confers greater benefit than that of aspirin or whether less intensive anticoagulation regimens would be equally effective with fewer bleeding complications. Patients at high risk for mural thrombus or with known mural thrombus should certainly be treated with systemic anticoagulation, initially with heparin and then with an oral anticoagulant.

Summary

In large part because of the interventions described in the preceding pages, the survival following hospital admission for acute MI has increased dramatically over the past 25 years. Survival over the first 30 days after hospital admission has risen from about 75% in 1970 to about 90% today.[60] Many therapeutic decisions faced by physicians, however, are not yet firmly grounded in the results of large, randomized, prospective clinical trials. There is still no substitute for sound and seasoned clinical judgment based on the assessment of each patient's condition.

Furthermore, the interactive effects among several interventions that are effective individually remain uncertain in many cases. Clearly, early thrombolytic therapy is a pivotal intervention to reduce mortality in acute MI. Percutaneous transluminal coronary angioplasty, if it can be performed expeditiously, may be an effective alternative to thrombolysis. The immediate use of aspirin and the early initiation of ACE inhibition have been shown to convey survival benefit with or without thrombolytic therapy. Long-term treatment with either aspirin or warfarin is indicated in suitable patients, but the optimal choice between these two drugs is not established. Immediate IV

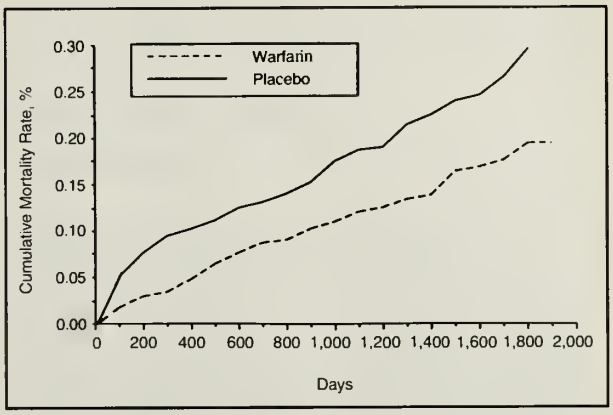

Figure 8.—A reduction in mortality after myocardial infarction is shown with warfarin therapy. The data are from the Warfarin Reinfarction Study. Much of the mortality reduction may be due to a reduced incidence of stroke (from Smith et al[56]).

β-blockade and the early use of nitrate preparations should be reserved for patients whose hemodynamic state or symptoms suggest a specific benefit; the ubiquitous application of these treatments has not been shown to reduce mortality, however. Because of the pronounced benefit of long-term oral β-blockade in reducing mortality after MI in trials done before the availability of thrombolytic therapy, it is reasonable to continue to use these agents. The benefit of long-term β-blockade is likely to be greatest in patients with reduced left ventricular function. We recommend the use of both a β-blocker and an ACE inhibitor, if tolerated. Antiarrhythmic drug therapy should be undertaken cautiously in patients who have had an MI and reserved primarily for patients with sustained, symptomatic, or hemodynamically compromising dysrhythmias. It is hoped that the role of amiodarone in these patients will be clarified by large, ongoing clinical trials.

REFERENCES

1. Reeder GS, Gersh BJ: Modern management of acute myocardial infarction. Curr Probl Cardiol 1993; 18:81-155

2. Naylor CD, Chen E: Population-wide mortality trends among patients hospitalized for acute myocardial infarction: The Ontario experience, 1981 to 1991. J Am Coll Cardiol 1994; 24:1431-1438

3. Pasternak RC, Braunwald E, Sobel BE: Acute myocardial infarction, *In* Braunwald E (Ed): Heart Disease. Philadelphia, Pa, WB Saunders, 1992, pp 1200-1291

4. Fuster V, Dyken ML, Vokonas PS, Hennekens C: Aspirin as a therapeutic agent in cardiovascular disease—Special Writing Group. Circulation 1993; 87:659-675

5. DeWood MA, Spores J, Notske R, et al: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980; 303:897-902

6. Kim CB, Braunwald E: Potential benefits of late reperfusion of infarcted myocardium—The open artery hypothesis. Circulation 1993; 88:2426-2436

7. Fibrinolytic Therapy Trialists' Collaborative Group: Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311-322

8. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) Investigators: Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1:397-402

9. Second International Study of Infarct Survival (ISIS-2) Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction. Lancet 1988; 2:349-360

10. Thrombolysis in Myocardial Infarct Study (TIMI IIIB) Investigators: Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non–Q-wave myocardial infarction—Results of the TIMI IIIB trial. Circulation 1994; 89:1545-1556

11. Muller DW, Topol EJ: Selection of patients with acute myocardial infarction for thrombolytic therapy. Ann Intern Med 1990; 113:949-960

12. Simoons ML, Maggioni AP, Knatterud G, et al: Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. Lancet 1993; 342: 1523-1528

13. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. Lancet 1993; 342:759-766

14. European Myocardial Infarction Project Group: Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N Engl J Med 1993; 329:383-389

15. Third International Study of Infarct Survival (ISIS-3) Collaborative Group—ISIS-3: A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. Lancet 1992; 339:753-770

16. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico—GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. Lancet 1990; 336:65-71

17. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329:673-682

18. Mark DB, Hlatky MA, Califf RM, et al: Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med 1995; 332:1418-1424

19. Simari RD, Berger PB, Bell MR, Gibbons RJ, Holmes DR Jr: Coronary angioplasty in acute myocardial infarction: Primary, immediate adjunctive, rescue, or deferred adjunctive approach? Mayo Clin Proc 1994; 69:346-358

20. Grines CL, Browne KF, Marco J, et al: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993; 328:673-679

21. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H: A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993; 328:680-684

22. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ: Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993; 328:685-691

23. Ellis SG, da Silva ER, Heyndrickx G, et al: Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994; 90: 2280-2284

24. Thrombolysis in Myocardial Infarction Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction—Results of the Thrombolysis in Myocardial Infarction (TIMI) phase II trial. N Engl J Med 1989; 320:618-627

25. SWIFT (Should We Intervene Following Thrombolysis?) Trial Study Group: SWIFT trial of delayed elective intervention versus conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. Br Med J 1991; 302:555-560

26. O'Neill WW: Angioplasty therapy of cardiogenic shock: Are randomized trials necessary? J Am Coll Cardiol 1992; 19:915-917

27. DeWood MA, Notske RN, Berg R, et al: Medical and surgical management of early Q wave myocardial infarction—I. Effects of surgical reperfusion on survival, recurrent myocardial infarction, sudden death and functional class at 10 or more years of follow-up. J Am Coll Cardiol 1989; 14:65-77

28. Sintek CF, Pfeffer TA, Khonsari S: Surgical revascularization after acute myocardial infarction—Does timing make a difference? J Thor Cardiovasc Surg 1994; 107:1317-1321

29. Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications—Effect of timing, dosage, and infarct location. Circulation 1988; 78:906-919

30. Yusuf S, Collins R, MacMahon S, Peto R: Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomised trials. Lancet 1988; 1:1088-1092

31. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico—GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994; 343:1115-1122

32. Fourth International Study of Infarct Survival (ISIS-4) Collaborative Group—ISIS-4: A randomised factorial trial assessing oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet 1995; 345:669-685

33. Metoprolol in Acute Myocardial Infarction (MIAMI) Trial Research Group: A randomised placebo-controlled international trial. Eur Heart J 1985; 6:199-226

34. First International Study of Infarct Survival Collaborative Group: Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986; 2:57-66

35. β-Blocker Heart Attack Trial Research Group: A randomized trial of propranolol in patients with acute myocardial infarction—I. Mortality results. JAMA 1982; 247:1707-1714

36. Pedersen TR: Six-year follow-up of the Norwegian Multicenter Study on Timolol after Acute Myocardial Infarction. N Engl J Med 1985; 313:1055-1058

37. Olsson G, Odén A, Johansson L, Sjögren A, Rehnqvist N: Prognosis after withdrawal of chronic postinfarction metoprolol treatment: A 2-7 year follow-up. Eur Heart J 1988; 9:365-372

38. Chadda K, Goldstein S, Byington R, Curb JD: Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986; 73:503-510

39. Furberg CD, Hawkins CM, Lichstein E: Effect of propranolol in postinfarction patients with mechanical or electrical complications. Circulation 1984; 69:761-765

40. Pfeffer MA, Braunwald E, Moye LA, et al: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction—Results of the Survival and Ventricular Enlargement trial. N Engl J Med 1992; 327:669-677

41. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342:821-828

42. Ambrosioni E, Borghi C, Magnani B: The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995; 332:80-85

43. Roberts R: Review of calcium antagonist trials in acute myocardial infarction. Clin Cardiol 1989; 12(suppl III):III-41–III-47

44. Danish Study Group on Verapamil in Myocardial Infarction: Verapamil in acute myocardial infarction. Eur Heart J 1984; 5:516-528

45. The effect of verapamil on mortality and major events after acute myocardial infarction: The Danish Verapamil Infarction Trial II (DAVIT II). Am J Cardiol 1990; 66:779-785

46. Multicenter Diltiazem Postinfarction Trial Research Group: The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988; 319:385-392

47. Gibson RS, Boden WE, Theroux P, et al: Diltiazem and reinfarction in patients with non–Q-wave myocardial infarction—Results of a double-blind, randomized, multicenter trial. N Engl J Med 1986; 315:423-429

48. Cassells W: Magnesium and myocardial infarction. Lancet 1994; 343: 807-809

49. Teo KK, Yusuf S, Collins R, Held PH, Peto R: Effects of intravenous magnesium in suspected acute myocardial infarction: Overview of randomised trials. Br Med J 1991; 303:1499-1503

50. Woods KL, Fletcher S, Roffe C, Haider Y: Intravenous magnesium sulphate in suspected acute myocardial infarction: Results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1992; 339:1553-1558

51. Wyse DG, Kellen J, Rademaker AW: Prophylactic versus selective lidocaine for early ventricular arrhythmias of myocardial infarction. J Am Coll Cardiol 1988; 12:507-513

52. Hine LK, Laird N, Hewitt P, Chalmers TC: Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. Arch Intern Med 1989; 149:2694-2698

53. Cardiac Arrhythmia Suppression Trial (CAST) Investigators: Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989; 321: 406-412

54. Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, et al: Effect of amiodarone on mortality after myocardial infarction: A double-blind, placebo-controlled, pilot study. J Am Coll Cardiol 1992; 20:1056-1062

55. Burkart F, Pfisterer M, Kiowski W, Follath F, Burckhardt D: Effect of antiarrhythmic therapy on mortality in survivors of myocardial infarction with asymptomatic complex ventricular arrhythmias: Basel Antiarrhythmic Study of Infarct Survival (BASIS). J Am Coll Cardiol 1990; 16:1711-1718

56. Smith P, Arnesen H, Holme I: The effect of warfarin on mortality and reinfarction after myocardial infarction. N Engl J Med 1990; 323:147-152

57. Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group: Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. Lancet 1994; 343:499-503

58. Asinger RW, Mikell FL, Elsperger J, Hodges M: Incidence of left-ventricular thrombosis after acute transmural myocardial infarction—Serial evaluation by two-dimensional echocardiography. N Engl J Med 1981; 305:297-302

59. Vaitkus PT, Barnathan ES: Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. J Am Coll Cardiol 1993; 22:1004-1009

60. Gomez-Marin O, Folsom AR, Kottke TE, et al: Improvement in long term survival among patients hospitalized with acute myocardial infarction, 1970 to 1980. N Engl J Med 1987; 316:1353-1359

Strategies for Preventing Type I Diabetes Mellitus

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Type I diabetes mellitus is a chronic autoimmune disease in which there is T cell-mediated destruction of the pancreatic beta cells. Susceptibility to the disease is determined by several genes, with HLA genes having the strongest effect. The onset of the disease is predictable, at least in the relatives of affected persons, using a combination of autoantibody measurements, intravenous glucose tolerance testing, and genetic typing. The disease may be preventable, and several large clinical trials are now underway to test whether interventions such as administering low-dose insulin or the use of nicotinamide can prevent the onset of diabetes in at-risk relatives.

(Verge CF, Eisenbarth GS: Strategies for preventing type I diabetes mellitus. West J Med 1996; 164:249-255)

Type I diabetes mellitus is a chronic autoimmune disease in which there is T cell-mediated destruction of the pancreatic beta cells.[1] The knowledge that type I diabetes is an autoimmune disorder is concordant with the relatively frequent association with additional autoimmune diseases, either in affected persons or other family members. These associated autoimmune diseases include hypothyroidism, Graves' disease, celiac disease, pernicious anemia, and Addison's disease.

First-degree relatives of patients with type I diabetes mellitus have an increased risk (about 6%) of diabetes developing.[2] Studies of autoantibody-positive relatives who have been observed to the onset of diabetes indicate that beta-cell autoimmunity may be evident for many years before the disease develops.[3-5] Thus, although the presentation with type I diabetes mellitus is often acute, it is now clear that its onset is preceded by a relatively long prediabetic period during which autoimmune beta-cell destruction occurs. Consequently, a window of opportunity exists during which intervention might preserve the remaining beta cells, thereby preventing diabetes and its long-term complications. If autoimmune beta-cell destruction could even be slowed, rather than completely suppressed, diabetes might be prevented from occurring during a person's lifetime.

Intervention trials depend on the ability to identify persons who are at increased risk for a progression to diabetes. Relatives at risk for type I diabetes mellitus can now be identified during the prediabetic period by a combination of tests. These currently include the measurement of autoantibodies, the measurement of first-phase insulin response with an intravenous glucose tolerance test (IVGTT), and HLA typing. We discuss a series of stages of "prediabetes" during which intervention may be effective, briefly review the tests used to identify at-risk persons, and describe the large-scale clinical trials that are currently underway.*

Stages of Prediabetes

Figure 1 shows a conceptual framework for stages in the development of type I diabetes mellitus. The usual time scale over which these stages proceed can be measured in years, although the existence of some cases of type I diabetes mellitus occurring in the first year of life indicates that this time scale may occasionally be compressed. Although it is likely that earlier intervention at a stage when the beta-cell mass is relatively intact may be more effective, the possible toxicity of any intervention needs to be balanced against the lesser degree of certainty with which high-risk persons can be identified early in the process.

Stage 1—Genetic Susceptibility

A susceptibility to type I diabetes mellitus is probably determined by several different genetic loci. Despite familial clustering of the disease, there is no identifiable mendelian pattern of inheritance. A first-degree relative has about a 10-fold to 15-fold increase in risk, even though 90% of persons in whom diabetes develops have no relative with the disease. Among the genetic loci implicated in type I diabetes, the HLA region on the short arm of chromosome 6 has the strongest effect.[6] No mutation resulting in a nonfunctioning gene product has been identified. Instead, polymorphisms (normal variants) of various genes are associated with susceptibility and resis-

*See also the editorial by J. Palmer, MD, "Prevention of Insulin-Dependent Diabetes Mellitus—Wishful Thinking, or Reality?" on pages 277-278 of this issue.

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ABBREVIATIONS USED IN TEXT

BCG = bacille Calmette-Guérin
DPT-1 = Diabetes Prevention Trial, Type 1
ENDIT = European-Canadian Nicotinamide Diabetes Intervention Trial
GAD = glutamic acid decarboxylase
ICA = islet cell autoantibodies
IGF-1 = insulin-like growth factor I
IVGTT = intravenous glucose tolerance test
JDF = Juvenile Diabetes Foundation
NAD = nicotinamide adenine dinucleotide
NOD = nonobese diabetic

tance. Serologic HLA typing indicates that susceptibility is associated with *DR3* and *DR4* haplotypes (Figure 2), whereas *DR3/DR4* heterozygosity confers the highest risk.[7] Molecular HLA typing has revealed many more alleles than could be distinguished by serologic typing. Each allele at each locus is now given a four-digit number—for example, *DQA1*0301*—that specifies a unique amino acid sequence.[8] Comparison of the haplotypes conferring susceptibility and resistance in different racial groups has suggested that susceptibility maps most closely to the *DQA1* and *DQB1* genes (Figure 2).[9-11] The products of these genes are α and β chains that come together to form the DQ molecule. DQ molecules have the function of presenting antigens to $CD4^+$ T cells. Determinants on both chains affect antigen binding, and it has been suggested that a number of combinations of *DQA1* and *DQB1* alleles are associated with a susceptibility to type 1 diabetes mellitus.[12] Molecular typing of HLA loci, including *DQA1* and *DQB1*, can readily be done using simple DNA probes.[13] HLA typing is useful as a marker of risk in the general population. At birth about 2% of American children carry the highest-risk genotype *DR3/DR4* (*DQA1*0501-DQB1*0201/DQA1*0301-DQB1*0302*). Such persons make up a third of all

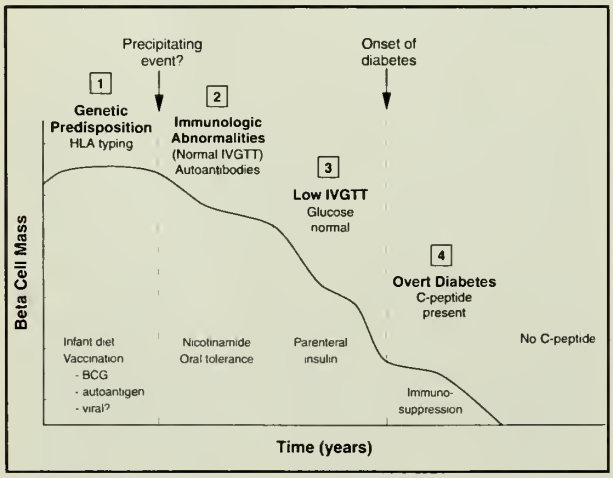

Figure 1.—The graph is a conceptual framework of stages in the development of type I diabetes mellitus in which beta-cell mass is plotted against time. At each stage, examples of possible interventions are listed that may be considered for a trial. BCG = bacille Calmette-Guérin, IVGTT = intravenous glucose tolerance test

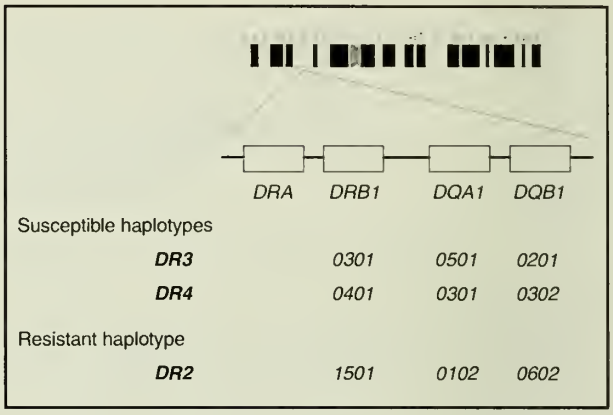

Figure 2.—The *HLA-DR* and *DQ* genes on the short arm of chromosome 6 are shown, indicating the common haplotypes of alleles conferring susceptibility and resistance to type I diabetes mellitus in whites. Serologic typing is shown in bold type, together with molecular typing at the *DRB1*, *DQA1*, and *DQB1* loci. The sequence of *DRA* is not polymorphic—that is, it is the same in everyone. The highest risk is conferred by the combination of *DR3* and *DR4* haplotypes, one inherited from each parent.

cases of type I diabetes mellitus[7] and have a risk equivalent to first-degree relatives of an affected person. In contrast, the *DR2* (*DQA1*0102-DQB1*0602*) haplotype confers strong protection from diabetes (Figure 2),[14] even in autoantibody-positive persons.[15]

Apart from HLA, a second genetic locus associated with type I diabetes mellitus is a polymorphism near the insulin gene on the short arm of chromosome 11.[16-18] This locus may be of less value in prediction because it has a considerably weaker effect than HLA, and the disease-associated allele is common in the general population. Additional loci, each with a relatively weak contribution to the familial clustering of diabetes, are being defined.

Environmental factors may be involved in precipitating or suppressing autoimmunity in genetically susceptible persons (see Figure 1). A role for environmental factors is suggested by the relatively low (about 35%) concordance for type I diabetes mellitus in identical twins,[19,20] although two thirds of long-term discordant twins have evidence of beta-cell autoimmunity.[21] Alternative explanations for the observed low concordance include the different T-cell repertoires of identical twins (due to a random rearrangement of T cell-receptor genes) and the possibility of somatic mutation at an unidentified susceptibility locus. Additional evidence implicating environmental factors in type I diabetes includes the increased incidence rates observed in certain migrant populations[22,23] and the rapidly rising incidence rates recently documented in several European countries,[24-30] too fast to be caused by an increased number of diabetogenic genes in the population.

Patients with congenital rubella have a markedly increased incidence of type I diabetes mellitus[31,32] and of thyroid autoimmunity.[33] A decreased CD4:CD8 ratio in patients with congenital rubella suggests that this infection may cause persisting alterations in the immune system.[34] Apart from congenital rubella, no specific

infection has yet been conclusively identified as a trigger for type I diabetes, although there are many suggestive reports.[35-38] In contrast, infections with a variety of pathogens nonspecifically reduce the incidence of diabetes in both animal models of autoimmune diabetes, the nonobese diabetic (NOD) mouse and the BB rat.[39] Perhaps in a similar manner, vaccination with complete Freund's adjuvant[40] or bacille Calmette-Guérin (BCG) (which contains complete Freund's adjuvant)[41] prevents diabetes in NOD mice, apparently by the induction of regulatory immune cells.[42-44]

Dietary factors have also been implicated in type I diabetes mellitus. The early introduction of artificial feeding in infancy has been associated with increased risk in several retrospective case-control studies.[45-48] In the BB rat model of autoimmune diabetes, adding cow's milk to the diet increases the incidence of the disease.[49]

Intervention at the stage of genetic susceptibility, before the appearance of any detectable immunologic abnormalities, might be based on screening cord blood for high-risk HLA genotypes. Low-toxicity interventions such as the removal of cow's milk from an infant's diet or BCG vaccination may be suitable for intervention at this early stage. The initial end point of such a trial could be the reduced appearance of autoantibodies in treated subjects. Studies in the offspring of diabetic parents have found that autoantibodies frequently appear in early infancy.[50] A Finnish trial will test the effect of excluding cow's milk proteins from the diet of infants who have a first-degree relative with type I diabetes mellitus.[51] A nonrandomized trial of BCG vaccination in 17 patients with newly diagnosed type I diabetes showed a higher rate of temporary remission than in historical controls, suggesting that the destruction of residual beta cells present at diagnosis may have been slowed.[41] The effect of BCG vaccination at an earlier stage has not yet been evaluated in humans. Vaccination to prevent a specific infection that triggers autoimmunity in genetically susceptible persons is another possibility, if such an infection could be identified. Finally, in animal models, "vaccination" with important autoantigens, such as a peptide fragment of the B chain of insulin[52] and glutamate decarboxylase (GAD),[53,54] prevents diabetes. Autoantigen vaccination for the prevention of diabetes is a pathway likely to be pursued.

Stage 2—Immunologic Abnormalities

In the second stage of prediabetes, immunologic abnormalities, including autoantibodies, appear (see Figure 1). The presence of high titers of islet cell autoantibodies (ICA) has proved to be the single most useful predictive test in screening relatives,[3,4,55] perhaps because antibodies directed against several different autoantigens within the islet can be detected simultaneously. Islet cell autoantibodies are measured by an indirect immunofluorescence assay, in which autoantibodies in a patient's serum bind to antigens present in frozen sections of normal human pancreas and are made visible on microscopy by fluorescently labeled anti-human immunoglobulin G. Serum specimens with a positive reaction are retested in serial dilutions to determine the end-point titer, which is converted to standard Juvenile Diabetes Foundation (JDF) units.[56]

The ICA assay is only semiquantitative, however, and has proved difficult to standardize, partly because of variation in the pancreatic substrate. Landin-Olsson found major differences in the ICA results obtained using five different pancreases in the same assay, despite standardization in JDF units.[57] In addition, a third of relatives progressing to diabetes during follow-up are negative for ICA on initial testing.[4] As an alternative, radioassays that measure autoantibodies directed against purified antigens are now available. These include assays for autoantibodies against insulin,[58] GAD,[59] and a tyrosine phosphatase molecule called ICA512 or IA2.[60-62] The measurement of antibodies against multiple biochemically characterized autoantigens by radioassay may soon replace the ICA assay. The radioassays have the advantages of high throughput and reproducibility. We have evaluated the use of three assays in combination: insulin, GAD, and ICA512. Preliminary data indicate that 98% of relatives progressing to diabetes have one or more of these autoantibodies. Relatives who have at least two of these antibodies have a high risk of progression to diabetes (68% within 5 years), whereas those with only a single autoantibody have a relatively low risk (15% within 5 years). This is consistent with the paradoxical finding that a subgroup of relatives strongly positive for ICA has a low risk of progression to diabetes. This subgroup has a particular pattern of ICA staining,[63,64] with antibodies reacting only with GAD and with no other autoantigen.[65]

Interventions suitable for stage 2 might include nicotinamide and oral antigen administration (oral tolerance). Nicotinamide, a B-group vitamin derived from nicotinic acid, protects the beta cell from free radicals that may be involved in autoimmune destruction. Free radicals, including nitric oxide, impair respiratory enzymes and cause DNA strand breaks. DNA strand breaks in turn are repaired by poly(ADP-ribose) polymerase, an enzyme that uses nicotinamide adenine dinucleotide (NAD) as a cofactor. Nicotinamide provides a source of NAD, and this is hypothesized to prevent cell death that would otherwise occur due to massive NAD depletion after free radical damage. In high concentration, it also inhibits poly(ADP-ribose) polymerase, further increasing the amount of NAD available to the beta cell. Thus, nicotinamide appears to act at the final stage of beta-cell destruction by ameliorating the effects of autoimmune attack.

Nicotinamide given early in life prevents diabetes in NOD mice,[66] but not in BB rats.[67] Several small randomized trials of nicotinamide administration in humans with newly diagnosed type I diabetes mellitus have been conducted, using C-peptide as an index of residual beta-cell function. These trials have produced conflicting results. One trial, using a dose of 3 grams per day, showed the preservation of C-peptide secretion compared with the placebo group,[68] but three others (using lower doses) found no significant difference.[69-71] No side effects were

observed except for recurrent diarrhea in a single patient.[68] Pilot data in autoantibody-positive relatives is limited. In one report, nicotinamide had no apparent effect in three ICA-positive relatives with abnormal results on IVGTTs, suggesting that nicotinamide may be ineffective if given late in the prediabetic period (stage 3 of Figure 1).[72] There was, however, some evidence for an effect, compared with historical controls, in a nonrandomized trial in which 14 ICA-positive children with abnormal IVGTTs received as much as 3 grams per day.[73] In another nonrandomized trial, ICA screening was offered to healthy children aged 5 to 7 years attending a subset (40%) of the schools in Auckland, New Zealand. Nicotinamide was given to those children found to be ICA-positive, and subsequently a lower-than-expected incidence of diabetes was reported among children attending the screened schools.[74]

The European-Canadian Nicotinamide Diabetes Intervention Trial (ENDIT) will test the ability of nicotinamide to prevent type I diabetes mellitus in a randomized, double-blind, placebo-controlled manner. Relatives with confirmed ICA will be randomly assigned to receive either nicotinamide or placebo. Although an IVGTT will be done before randomization, the results will not be an entry criterion. It is planned to enroll 528 ICA-positive subjects, giving 90% power to detect a 40% reduction in progression to diabetes over five years of follow-up, with allowance for a 20% dropout rate. Compliance will be assessed by the measurement of urinary metabolites of nicotinamide. The dose of nicotinamide (1.2 grams per m^2 per day in a sustained-release preparation) is 100 to 150 times the recommended daily intake. Toxicity studies in rats found no evidence of malignancy—despite a theoretical risk due to the inhibition of DNA repair enzymes—but did report impaired growth with a dose equivalent to 40 times the ENDIT dose. In humans, only minor side effects have been reported, including a reversible elevation of liver enzyme levels.

Intermittent oral administration of insulin to NOD mice from birth has been shown to delay the onset of diabetes and to reduce the degree of insulitis.[75] Oral tolerance is effective in many other animal models of autoimmunity, including collagen-induced arthritis, experimental allergic encephalomyelitis (a model of multiple sclerosis), experimental allergic uveoretinitis, and adjuvant arthritis. The induction of tolerance by administering oral antigen is antigen-specific and appears to involve not only active suppression and clonal anergy but also extrathymic deletion of antigen-reactive T cells.[76,77] The effect appears to be sensitive to the dose of antigen given, as increasing the dose of insulin administered to NOD mice from 1 mg to 5 mg abolished the protective effect. Similar dose-dependency has been observed for oral myelin basic protein in experimental allergic encephalitis and oral collagen in collagen-induced arthritis. In a randomized, placebo-controlled trial of oral myelin administration to humans with multiple sclerosis, 6 of 15 patients in the treated group had a disease exacerbation, compared with 12 of 15 in the control group ($P = .06$).[78]

Stage 3—Measurable Loss of Insulin Secretion

The progressive loss of beta-cell mass is eventually reflected by changes in insulin secretion that can be detected with an IVGTT well before the onset of diabetes. The first-phase insulin response is usually defined as the sum of the plasma insulin levels at one minute and three minutes after a standard glucose infusion during an IVGTT. Although a standard protocol for the IVGTT has been developed,[79] the first-phase insulin response has a within-subject coefficient of variation of about 20%.[80,81] In normal subjects, the first-phase insulin response may vary with age,[82] physical fitness,[83] body mass index, and pubertal status.[79] Despite this variation, a low first-phase insulin response (below the first percentile of controls) in an autoantibody-positive relative is highly predictive of subsequent progression to diabetes.[84]

With increased certainty of the risk of progression to diabetes, interventions with a slightly greater risk of adverse effects can be contemplated, including injecting low doses of insulin. The subcutaneous administration of insulin prevents diabetes in both the NOD mouse and BB rat models of autoimmune diabetes.[85,86] Possible mechanisms include beta-cell rest and the induction of tolerance. Beta-cell rest refers to the situation in which exogenous insulin reduces endogenous insulin secretion, reducing the expression of beta-cell antigens,[87] and perhaps protecting the beta cell from the effects of autoimmune attack. Studies in NOD mice, however, have shown that administering the (metabolically inactive) insulin B chain also protects from diabetes, whereas administering the A chain does not.[85] This suggests that the induction of tolerance is important. Furthermore, T cells from injected animals were able to transfer protection to other animals, suggesting that the mechanism involves an active suppression of immune responses to epitopes on the insulin B chain. The insulitis score was not decreased, but interferon-gamma levels within the islet were reduced, consistent with a nondestructive form of insulitis.[85] Additional evidence for an immunologic effect comes from an experiment in which NOD mice were administered either insulin or insulin-like growth factor-I (IGF-I) in doses with equivalent hypoglycemic effects. It was found that insulin protected from diabetes but that IGF-I did not.[88]

In humans, administering insulin intravenously for two weeks at the onset of type I diabetes mellitus resulted in the preservation of higher C-peptide secretion for at least a year than in controls receiving conventional insulin therapy.[89] A nonrandomized, open pilot trial of injecting insulin in ICA-positive relatives has suggested a substantial protective effect.[90] Insulin was offered to 12 high-risk relatives, of whom 5 accepted, and the treated subjects received twice-a-day extended insulin zinc suspension (Ultralente) subcutaneously. The dose—initially 0.25 units per kg per day—was adjusted to avoid hypoglycemia, but there was no dietary modification or home blood glucose monitoring. No severe hypoglycemia with altered consciousness was reported in the treated group.

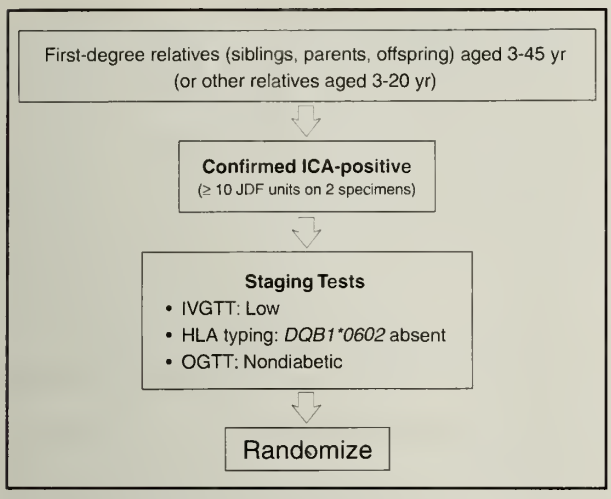

Figure 3.—Eligibility criteria are shown for the nationwide National Institutes of Health trial of the use of parenteral insulin (Diabetes Prevention Trial, Type I). ICA = islet-cell autoantibodies, IVGTT = intravenous glucose tolerance testing, JDF = Juvenile Diabetes Foundation, OGTT = oral glucose tolerance test

In addition, these subjects received five-day courses of continuous intravenous insulin—about 0.02 units per kg per day—in a hospital every nine months. With follow-up times ranging from 2.3 to 3.7 years, diabetes developed in one of five treated relatives compared with all seven untreated relatives.

The ability of parenteral insulin to prevent or delay the onset of type I diabetes mellitus is currently being evaluated in the United States in a multicenter National Institutes of Health trial, the Diabetes Prevention Trial, Type I (DPT-I). It is planned to screen 60,000 first-degree relatives (siblings, parents, and offspring aged 3 to 45 years) of patients with type I diabetes mellitus for ICA (Figure 3). Other relatives, if aged 3 to 20, are also eligible to be screened. Those with ICA levels of greater than 10 JDF units (confirmed with a second specimen, or on 2 out of 3 specimens if the first 2 are not concordant) will be further evaluated with IVGTT, molecular HLA typing, and an oral glucose tolerance test. Subjects with the protective HLA allele *DQB1*0602* or with a diabetic oral glucose tolerance test (by adult criteria[91]) will be excluded from the trial. Those with a first-phase insulin response on IVGTT less than the 10th percentile of controls (confirmed on 2 occasions) have a greater than 50% probability of diabetes developing within five years and will be randomly selected to receive either insulin, in a manner similar to the earlier-described pilot trial, or no treatment (observation-only arm). The use of placebo injections in children was not ethically justifiable. It is planned to randomly assign 170 subjects to each arm, giving 80% power to detect a 35% decrease in progression to diabetes, after allowing for a 10% dropout rate and a 10% noncompliance rate.

Stage 4—Overt Diabetes

Progressive beta-cell destruction leads to the onset of overt diabetes when the beta-cell mass is reduced to about 20% of normal.[92] The presence of residual functioning beta cells explains the remission or "honeymoon" phase that frequently occurs soon after the start of insulin therapy in most patients. During this phase, immunosuppressive agents have been evaluated, aiming to prolong remission. The preservation of C-peptide secretion is the usual outcome measure.

The administration of cyclosporine increases the rate and length of remissions in recently diagnosed cases,[93-95] although the remissions are of limited duration (no longer than 2 years[96]) and the therapy carries a risk of nephrotoxicity. A randomized, placebo-controlled trial of azathioprine treatment found no difference in insulin requirements or stimulated C-peptide levels.[97] Another trial of the use of azathioprine and prednisone in combination, however, found a higher rate of insulin-free remission and higher stimulated C-peptide levels after a year of treatment.[98] The effects of immunosuppressive therapy were greater in subjects with higher C-peptide levels at diagnosis,[96] that is, those with greater residual beta-cell mass. As detailed in the preceding sections, other interventions, including the use of BCG vaccination and of nicotinamide, have also been evaluated in newly diagnosed patients, and it is likely that trials of oral tolerance and antigen-specific vaccination will also be initiated in this group.

Conclusion

With the use of autoantibody screening, intravenous glucose tolerance testing, and HLA typing, it is now possible to identify a group of relatives who have a sufficiently high risk of diabetes to warrant intervention trials. Approximately 90% of patients with newly diagnosed type I diabetes mellitus do not have an affected relative, indicating that programs to screen the general population will be required if an effective intervention is found. Preliminary data suggest that autoantibody testing will be predictive in the general population as well as among relatives.[99] Large-scale randomized trials are now underway to determine whether diabetes can be prevented or delayed in autoantibody-positive first-degree relatives. We recommend autoantibody screening for all relatives of patients with type I diabetes mellitus. Physicians or relatives who would like to receive further information about the DPT-I or a blood screening kit can telephone the coordinating center at 1-800-HALT-DM1.

REFERENCES

1. Eisenbarth GS: Type I diabetes mellitus: A chronic autoimmune disease. N Engl J Med 1986; 314:1360-1368

2. Tillil H, Kobberling J: Age-correlated empirical genetic risk estimates for first degree relatives of IDDM patients. Diabetes 1987; 36:93-99

3. Bonifacio E, Bingley PJ, Shattock M, et al: Quantification of islet-cell antibodies and prediction of insulin-dependent diabetes. Lancet 1990; 335:147-149

4. Riley WJ, Maclaren NK, Krischer J, et al: A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. N Engl J Med 1990; 323:1167-1172

5. Srikanta S, Ganda OP, Soeldner JS, Eisenbarth GS: First degree relatives of patients with type I diabetes mellitus: Islet cell antibodies and abnormal insulin secretion. N Engl J Med 1985; 313:461-464

6. Davies JL, Kawaguchi Y, Bennett ST, et al: A genome-wide search for human type I diabetes susceptibility genes. Nature 1994; 371:130-136

7. Thomson G, Robinson WP, Kuhner MK, et al: Genetic heterogeneity, modes of inheritance, and risk estimates for a joint study of Caucasians with insulin-dependent diabetes mellitus. Am J Hum Genet 1988; 43:799-816

8. Bodmer JG, Marsh SGE, Albert ED, et al: Nomenclature for factors of the HLA system, 1995. Hum Immunol 1995; 43:149-164

9. Fletcher J, Mijovic C, Odughesan O, Jenkins D, Bradwell AR, Barnett AH: Trans-racial studies implicate HLA-DQ as a component of genetic susceptibility to type I (insulin-dependent) diabetes. Diabetologia 1988; 31:864-870

10. Todd JA, Mijovic C, Fletcher J, Jenkins D, Bradwell AR, Barnett AH: Identification of susceptibility loci for insulin-dependent diabetes mellitus by trans-racial gene mapping. Nature 1989; 338:587-589

11. Jenkins D, Mijovic C, Fletcher J, Jacobs KH, Bradwell AR, Barnett AH: Identification of susceptibility loci for type I (insulin-dependent) diabetes by trans-racial gene mapping. Diabetologia 1990; 33:387-395

12. Rønningen KS, Spurkland A, Iwe T, Vartdal F, Thorsby E: Distribution of HLA-DRB1, -DQA1 and -DQB1 alleles and DQA1-DQB1 genotypes among Norwegian patients with insulin-dependent diabetes mellitus. Tissue Antigens 1991; 37:105-111

13. Bugawan L, Erlich HA: Rapid typing of HLA-DQB1 DNA polymorphism using nonradioactive oligonucleotide probes and amplified DNA. Immunogenetics 1991; 33:163-170

14. Baisch JM, Weeks T, Giles R, Hoover M, Stastny P, Capra JD: Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. N Engl J Med 1990; 322:1836-1841

15. Pugliese A, Gianani R, Moromisato R, et al: HLA-DQB1*0602 is associated with dominant protection from diabetes even among islet cell antibody positive first degree relatives of patients with insulin-dependent diabetes. Diabetes 1995; 44:608-613

16. Bell GI, Horita S, Karam JH: A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. Diabetes 1984; 33:176-183

17. Julier C, Hyer RN, Davies J, et al: Insulin-IGF2 region encodes a gene implicated in HLA-DR4-dependent diabetes susceptibility. Nature 1991; 354: 155-159

18. Bennett ST, Lucassen AM, Gough SCL, et al: Susceptibility to human type I diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. Nature Genet 1995; 9:284-292

19. Olmos P, A'Hern R, Heaton DA, et al: The significance of concordance rate for type I (insulin-dependent) diabetes mellitus in identical twins. Diabetologia 1988; 31:747-750

20. Kaprio J, Tuomilehto J, Koskenvuo M, et al: Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland. Diabetologia 1992; 35:1060-1067

21. Verge CF, Gianani R, Yu L, et al: Late progression to diabetes and evidence for chronic beta cell autoimmunity in identical twins of patients with type I diabetes. Diabetes 1995; 44:1176-1179

22. Bodansky HJ, Staines A, Stephenson C, Haigh D, Cartwright R: Evidence for an environmental effect in the aetiology of insulin dependent diabetes in a transmigratory population. Br Med J 1992; 304:1020-1022

23. Elliott RB, Pilcher C, Edgar BW: Geographic IDDM in Polynesia and Macronesia: The Epidemiology of Insulin Dependent Diabetes in Polynesian Children Born and Reared in Polynesia, Compared With Polynesian Children Resident in Auckland, New Zealand—Diabetes in the Young Bulletin. Proceedings of the International Study Group for Diabetes (Abstr) 1989; 20:16

24. Rewers M, LaPorte RE, Walczak M, Dmochowski K, Bogaczynska E: Apparent epidemic of insulin-dependent diabetes mellitus in midwestern Poland. Diabetes 1987; 36:106-113

25. Green A, Andersen PK, Svendsen AJ, Mortensen K: Increasing incidence of early onset type I (insulin-dependent) diabetes mellitus: A study of Danish male birth cohorts. Diabetologia 1992; 35:178-182

26. Tuomilehto J, Rewers M, Reunanen A, et al: Increasing trend in type I (insulin-dependent) diabetes mellitus in childhood in Finland: Analysis of age, calendar time, and birth cohort effects during 1965 to 1984. Diabetologia 1991; 34:282-287

27. Joner G, Søvik O: Increasing incidence of diabetes mellitus in Norwegian children 0-14 years of age 1973-1982. Diabetologia 1989; 32:79-83

28. Nyström L, Dahlquist G, Rewers M, Wall S: The Swedish childhood diabetes study—An analysis of the temporal variation in diabetes incidence, 1978-1987. Int J Epidemiol 1990; 19:141-146

29. Soltész G, Madácsy L, Békefi D, Dankó I: Rising incidence of type I diabetes in Hungarian children (1978-1987)—Hungarian Childhood Diabetes Epidemiology Group. Diabetic Med 1989; 7:111-114

30. Drykoningen CEM, Mulder ALM, Vaandrager GJ, LaPorte RE, Bruining GJ: The incidence of male childhood type I (insulin-dependent) diabetes mellitus is rising rapidly in The Netherlands. Diabetologia 1992; 35:139-142

31. Menser MA, Forrest JM, Bransby RD: Rubella infection and diabetes mellitus. Lancet 1978; 1:57-60

32. Karounos DG, Simmerman L, Hickman SL, Jacob RJ: Identification of the p52-rubella related autoantigen as an insulin secretory granule protein (Abstr). Diabetes 1993; 42(suppl 1):221A

33. Clarke WL, Shaver KA, Bright GA, Rogal AD, Nance WE: Autoimmunity in congenital rubella syndrome. J Pediatr 1984; 104:370-373

34. Rahinowe SL, George KL, Laughlin R, Soeldner JS, Eisenharth GS: Congenital rubella: Monoclonal antibody-defined T cell ahnormalities in young adults. Am J Med 1986; 81:779-782

35. Oldstone M, Nerenberg M, Southern P, Price J, Lewicki H: Virus infection triggers insulin-dependent diabetes mellitus in a transgenic model: Role of anti-self (virus) immune response. Cell 1991; 65:319-331

36. Yoon JW, Austin M, Onodera T, Notkins AL: Virus-induced diabetes mellitus: Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. N Engl J Med 1979; 300:1173-1179

37. Ohashi PS, Oehen S, Buerki K, et al: Ablation of 'tolerance' and induction of diabetes by virus infection in viral antigen transgenic mice. Cell 1991; 65: 305-317

38. Yoon JW: Role of viruses in the pathogenesis of IDDM. Ann Med 1991; 23:437-445

39. Oldstone MBA: Prevention of type I diabetes in nonobese diabetic mice by virus infection. Science 1988; 239:500-502

40. McInerney MF, Pek SB, Thomas DW: Prevention of insulitis and diabetes onset by treatment with complete Freund's adjuvant in NOD mice. Diabetes 1991; 40:715-725

41. Shehadeh N, Calcinaro F, Bradley BJ, Bruchlim I, Vardi P, Lafferty KJ: Effect of adjuvant therapy on development of diabetes in mouse and man. Lancet 1994; 343:706-707

42. Qin H, Sadelain MWJ, Hitchon C, Lauzon J, Singh B: Complete Freund's adjuvant-induced T cells prevent the development and adoptive transfer of diabetes in non-obese diabetic mice. J Immunol 1993; 150:2072-2080

43. Yagi H, Matsumoto M, Suzuki S, et al: Possible mechanism of the preventive effect of BCG against diabetes mellitus in NOD mouse—I. Generation of suppressor macrophages in spleen cells of BCG-vaccinated mice. Cell Immunol 1991; 138:130-141

44. Yagi H, Matsumoto M, Kishimoto Y, Makino S, Harada M: Possible mechanism of the preventive effect of BCG against diabetes mellitus in NOD mouse—II. Suppression of pathogenesis by macrophage transfer from BCG-vaccinated mice. Cell Immunol 1991; 138:142-149

45. Virtanen SM, Rasanen L, Aro A, et al: Infant feeding in Finnish children < 7 yr of age with newly diagnosed IDDM. Diabetes Care 1991; 14:415-417

46. Verge CF, Howard NJ, Irwig L, Simpson JM, Mackerras D, Silink M: Environmental factors in childhood IDDM: A population-based, case-control study. Diabetes Care 1994; 17:1381-1389

47. Mayer EJ, Hamman RF, Gay EC, Lezotte DC, Savitz DA, Klingensmith GJ: Reduced risk of IDDM among breast-fed children—The Colorado IDDM registry. Diabetes 1988; 37:1625-1632

48. Kostraba JN, Cruickshanks KJ, Lawler-Heavner J, et al: Early exposure to cow's milk and solid foods in infancy, genetic predisposition, and risk of IDDM. Diabetes 1993; 42:288-295

49. Elliott RB, Martin JM: Dietary protein: A trigger of insulin-dependent diabetes in the BB rat? Diabetologia 1984; 26:297-299

50. Ziegler AG, Hillebrand B, Rabl W, et al: On the appearance of islet associated autoimmunity in offspring of diabetic mothers: a prospective study from birth. Diabetologia 1993; 36:402-408

51. Akerblom HK, Paganus A, Teramo K, et al: Primary prevention of type I diabetes by nutritional intervention—Description of a pilot study (Abstr). Autoimmunity 1993; 15(suppl):58

52. Wegman DR, Norbury-Glaser M, Daniel D: Insulin-specific T cells are a predominant component of islet infiltrates in pre-diabetic NOD mice. Eur J Immunol 1994; 24:1853-1857

53. Kaufman DL, Clare-Salzler M, Tian J, et al: Spontaneous loss of T-cell tolerance to glutamic acid decarboxylase in murine insulin-dependent diabetes. Nature 1993; 366:69-72

54. Tisch R, Yang X, Singer SM, Liblau RS, Fugger L, McDevitt HO: Immune response to glutamic acid decarboxylase correlates with insulitis in non-obese diabetic mice. Nature 1993; 366:72-75

55. Srikanta S, Ganda OP, Eisenbarth GS, Soeldner JS: Islet cell antibodies and beta-cell function in monozygotic triplets and twins initially discordant for type I diabetes mellitus. N Engl J Med 1983; 308:322-325

56. Greenbaum CJ, Palmer JP, Nagataki S, et al: Improved specificity of ICA assays in the Fourth International Immunology of Diabetes Exchange Workshop. Diabetes 1992; 41:1570-1574

57. Landin-Olsson M: Precision of the islet-cell antibody assay depends on the pancreas. J Clin Lab Anal 1990; 4:289-294

58. Palmer JP, Asplin CM, Clemons P, et al: Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science 1983; 222:1337-1339

59. Baekkeskov S, Aanstoot HJ, Christgau S, et al: Identification of the 64K autoantigen in insulin dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature 1990; 347:151-156

60. Rabin DU, Pleasic SM, Shapiro JA, et al: Islet cell antigen 512 is a diabetes-specific islet autoantigen related to protein tyrosine phosphatases. J Immunol 1994; 152:3183-3188

61. Lan MS, Lu J, Goto Y, Notkins AL: Molecular cloning and identification of a receptor-type protein tyrosine phosphatase, IA-2, from human insulinoma. DNA Cell Biol 1994; 13:505-514

62. Gianani R, Yu L, Verge CF, Babu S, Pietropaolo M, Eisenbarth GS: Recombinant ICA512 radioassay (Abstr). J Invest Med 1995; 43(suppl):331A

63. Gianani R, Pugliese A, Bonner-Weir S, et al: Prognostically significant heterogeneity of cytoplasmic islet cell antibodies in relatives of patients with type I diabetes. Diabetes 1992; 41:347-353

64. Genovese S, Bonifacio E, McNally JM, et al: Distinct cytoplasmic islet cell antibodies with different risks for type I (insulin-dependent) diabetes mellitus. Diabetologia 1992; 35:385-388

65. Gianani R, Jackson R, Eisenbarth GS: Evidence that the autoantigen of restricted ICA is GAD (Abstr). Diabetes Res Clin Pract 1991; 14(suppl 1):S13

66. Yamada K, Nonaka K, Hanafusa T, Miyazaki A, Toyoshima H, Tarui S: Preventive and therapeutic aspects of large-dose nicotinamide injections on diabetes associated with insulitis: An observation in non-obese diabetic (NOD) mice. Diabetes 1982; 31:749-753

67. Hermitte L, Vialettes B, Atlef N, et al: High dose nicotinamide fails to prevent diabetes in BB rats. Autoimmunity 1989; 5:79-86

68. Vague P, Picq R, Bernal M, Lassmann-Vague V, Vialettes B: Effect of nicotinamide treatment on the residual insulin secretion in type I (insulin-dependent) diabetic patients. Diabetologia 1989; 32:316-321

69. Mendola G, Casamitjana R, Gomis R: Effect of nicotinamide therapy upon B-cell function in newly diagnosed type 1 (insulin-dependent) diabetic patients. Diabetologia 1989; 32:160-162

70. Chase HP, Butler-Simon N, Garg S, McDuffie M, Hoops SL, O'Brien D: A trial of nicotinamide in newly diagnosed patients with type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990; 33:444-446

71. Lewis CM, Canafax DM, Sprafka JM, Barbosa JJ: Double-blind randomized trial of nicotinamide on early-onset diabetes. Diabetes Care 1992; 15:121-123

72. Herskowitz RD, Jackson RA, Soeldner JS, Eisenbarth GS: Pilot trial to prevent type I diabetes: Progression to overt IDDM despite oral nicotinamide. J Autoimmunity 1989; 2:733-737

73. Elliott RB, Chase HP: Prevention or delay of type I (insulin-dependent) diabetes mellitus in children using nicotinamide. Diabetologia 1991; 34:362-365

74. Elliott RB, Pilcher CC, McGregor MA: Protection from diabetes in normal school children using nicotinamide (Abstr). Autoimmunity 1993; 15 (suppl):57

75. Zhang JZ, Davidson L, Eisenbarth GS, Weiner HL: Suppression of diabetes in nonobese diabetic mice by oral administration of porcine insulin. Proc Natl Acad Sci USA 1991; 88:10252-10256

76. Thompson HSG, Staines NA: Could specific oral tolerance be a therapy for autoimmune disease? Immunol Today 1990; 11:396-399

77. Chen Y, Inobe J, Marks R, Gonnella P, Kuchroo VK, Weiner HL: Peripheral deletion of antigen-reactive T cells in oral tolerance. Nature 1995; 376: 177-180

78. Weiner HL, Mackin GA, Matsui M, et al: Double-blind pilot trial of oral tolerization with myelin antigens in multiple sclerosis. Science 1993; 259: 1321-1324

79. Bingley PJ, Colman P, Eisenbarth GS, et al: Standardization of IVGTT to predict IDDM. Diabetes Care 1992; 15:1313-1316

80. Colman PG, Stewart V, Kean J, et al: Comparison of two commonly used standard IVGTTs. Diabetes Care 1992; 15:1053-1055

81. Allen HF, Jeffers BW, Klingensmith GJ, Chase HP: First-phase insulin release in normal children. J Pediatr 1993; 123:733-738

82. Carel JC, Boitard C, Bougnères PF: Decreased insulin response to glucose in islet cell antibody-negative siblings of type 1 diabetic children. J Clin Invest 1993; 92:509-513

83. Arslanian S, Austin A: Determinants of first and second phase insulin secretion in healthy adolescents (Abstr). Pediatr Res 1993; 3(suppl):S74

84. Vardi P, Crisa L, Jackson RA: Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than the first percentile in islet cell antibody positive relatives of type 1 (insulin-dependent) diabetic patients. Diabetologia 1991; 34:93-102

85. Muir A, Peck A, Clare-Salzler M, et al: Insulin immunization of nonobese diabetic mice induces a protective insulitis characterized by diminished intraislet interferon-gamma transcription. J Clin Invest 1995; 95:628-634

86. Gotfredsen CF, Buschard K, Frandsen EK: Reduction of diabetes incidence of BB Wistar rats by early prophylactic insulin treatment of diabetes-prone animals. Diabetologia 1985; 28:933-935

87. Björk E, Kämpe O, Andersson A, Karlsson FA: Expression of the 64 kDa/glutamic acid decarboxylase rat islet cell autoantigen is influenced by the rate of insulin secretion. Diabetologia 1992; 32:490-493

88. Elliott RB, Bibby NJ, Ambler G: Prevention of diabetes in the NOD mouse by insulin is unrelated to its metabolic effect (Abstr). Autoimmunity 1993; 15(suppl):71

89. Shah SC, Malone JI, Simpson NE: A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 1989; 320:550-554

90. Keller RJ, Eisenbarth GS, Jackson RA: Insulin prophylaxis in individuals at high risk of type I diabetes. Lancet 1993; 341:927-928

91. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28:1039-1057

92. McCulloch DK, Koerker DJ, Kahn SE, Bonner-Weir S, Palmer JP: Correlations of in vivo beta-cell function tests with beta-cell mass and pancreatic insulin content in streptozocin-treated baboons. Diabetes 1991; 40:673-679

93. Feutren G, Papoz L, Assan G, et al: Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset—Results of a multicentre double-blind trial. Lancet 1986; 2:119-124

94. Dupre J, Jenner MR, Mahon JL, Purdon C, Rodger NW, Stiller CR: Endocrine-metabolic function in remission-phase IDDM during administration of cyclosporine. Diabetes 1991; 40:598-604

95. Martin S, Schernthaner G, Nerup J, et al: Follow-up of cyclosporin A treatment in type 1 (insulin-dependent) diabetes mellitus: Lack of long-term effects. Diabetologia 1991; 34:429-434

96. Bougnères PF, Landais P, Boisson C, et al: Limited duration of remission of insulin dependency in children with recent overt type 1 diabetes treated with low-dose cyclosporine. Diabetes 1990; 39:1264-1272

97. Cook JJ, Hudson I, Harrison LC, et al: Double blind controlled trial of azathioprine in children with newly diagnosed type I diabetes. Diabetes 1989; 38: 779-783

98. Silverstein J, Maclaren N, Riley W, Spillar R, Radjenovic D, Johnson S: Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. N Engl J Med 1988; 319:599-604

99. Schatz D, Krischer J, Horne G, et al: Islet cell antibodies predict insulin-dependent diabetes in United States school age children as powerfully as in unaffected relatives. J Clin Invest 1994; 93:2403-2407

Epitomes

Important Advances in Psychiatry

Psychiatry

Victor I. Reus, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under the direction of Victor I. Reus, MD, and the panel.

Magnetic Resonance Spectroscopy and Psychiatry

With the availability of in vivo high-resolution magnetic resonance spectroscopy (MRS), it is now possible to study directly and noninvasively the chemistry and metabolism of human brain tissue. Magnetic resonance spectroscopy has tremendous potential for detecting specific neurobiologic abnormalities underlying the major psychiatric disorders. Because the procedure is done with the same magnet that is used for magnetic resonance imaging, there is an excellent opportunity to study regional brain structure and function simultaneously with both procedures.

Magnetic resonance spectroscopy can be used to study the resonance spectra of compounds in the brain that contain odd-numbered nuclei such as hydrogen 1, lithium 7, carbon 13, oxygen 17, fluorine 19, sodium 23, magnesium 25, and phosphorus 31. Because the technology uses magnetism and radio waves rather than ionizing radiation or radioactive tracers, it is considered safer than positron-emission tomography (PET) or single-photon-emission computed tomography (SPECT). The relative cost of an MRS study is comparable to a SPECT study and less expensive than a PET study. In addition, because MRS can be safely repeated numerous times, it is an ideal technique for assessing longitudinal changes in brain metabolism. Studies using ^{31}P, for example, yield information about high-energy phosphate compounds such as adenosine triphosphate and phosphocreatine, as well as phospholipid metabolism (phosphomonoesters and phosphodiesters). If proton spectra are obtained, information about psychiatrically relevant compounds such as lactate, glutamate, aspartate, γ-aminobutyric acid (GABA), creatine, choline, and *N*-acetylaspartate (a putative neuronal marker) can be obtained from any specific brain region. Such a window into the chemistry of the living brain of patients with psychiatric disorders is clearly unprecedented. These characteristics are why MRS studies of the brain have been referred to as "noninvasive biopsies" of brain tissue.

Recent MRS investigations of psychiatric disorders such as schizophrenia and bipolar disorder using ^{31}P have yielded results suggesting alterations in both brain high-energy phosphate and membrane phospholipid metabolism in the frontal and temporal lobes. In some studies, these alterations have been associated with the severity of clinical symptoms. Proton (^{1}H) MRS studies in schizophrenia, bipolar disorder, and depression have also yielded valuable information regarding changes in metabolites such as *N*-acetylaspartate, choline, and creatine. The changes in *N*-acetylaspartate are particularly noteworthy because they suggest decreases in the neuronal density of certain brain regions. Some studies have also documented alterations in glutamate, aspartate, and GABA levels in the frontal brain regions of patients with schizophrenia. Magnetic resonance spectroscopic investigations in patients with autism and various forms of dementia using ^{1}H and ^{31}P have also elicited interesting findings.

Finally, in vivo ^{1}H, ^{7}Li, ^{13}C, ^{19}F, or ^{31}P MRS can be used for pharmacologic studies of the human brain either through the direct measurement of drug concentrations or of drug effects on brain metabolism. Perhaps most exciting for psychiatry is that MRS using ^{19}F has measured the human brain concentrations of fluorinated psychoactive drugs such as fluphenazine, trifluoperazine, and fluoxetine. In a similar manner, MRS using ^{7}Li and ^{31}P has measured the human brain concentrations of lithium and demonstrated effects of lithium on phospholipid metabolism.

It is clear that as the field of in vivo MRS develops, it will contribute to major advances in identifying neurobiologic abnormalities in psychiatric disorders that are perhaps too subtle to detect by other methods. It is hoped that this technology will also help to facilitate the monitoring and metabolic effects of pharmacologic and other treatment modalities in these disorders. At present, it has not been determined how MRS studies will be used in the clinical setting.

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REFERENCES

Dager SR, Steen RG: Applications of magnetic resonance spectroscopy to the investigation of neuropsychiatric disorders. Neuropsychopharmacology 1992; 6:249-266

Klunk WE, Keshavan M, Panchalingam K, Pettegrew JW: Magnetic resonance spectroscopy: Applications to neuropsychiatric research, *In* Oldham JM, Riba MB, Tasman A (Eds): American Psychiatric Press Review of Psychiatry—Vol 12. Washington, DC, American Psychiatric Press, 1993, pp 383-420

Nasrallah HA, Pettegrew JW (Eds): Progress in Psychiatry Series #47: NMR Spectroscopy in Psychiatric Brain Disorders. Washington, DC, American Psychiatric Press, 1995

Risperidone—A New Antipsychotic Agent

RISPERIDONE is the first antipsychotic agent designed to antagonize both dopamine and serotonin receptors as does clozapine. Unlike clozapine, it has little effect on cholinergic and β-adrenergic receptors but does affect α_2-adrenergic and histamine H_1 receptors.

In a series of controlled studies, risperidone has been shown to be an active antipsychotic agent in doses ranging from 4 to 16 mg. Dosages greater than 6 mg have not shown greater activity, but have more side effects, including extrapyramidal signs. The use of a dose of 6 mg was shown to be superior to both a placebo and 20 mg of haloperidol and with no difference in extrapyramidal effects compared with the placebo. Thus, at this dosage, a beneficial effect was seen in both "positive" (such as delusions and hallucinations) and "negative" (such as emotional withdrawal and blunted affect) symptoms with a minimum of extrapyramidal signs. This led to the suggestion of the rapid titration of this dosage for everyone, but clinical experience has shown this to be a mistake. First (and apart from its cost), not all patients require 6 mg. Second, although there was no group difference between the use of 6 mg and a placebo, extrapyramidal signs do develop in some persons at this dosage, with dystonic reactions reported at dosages as low as 2 mg. It appears now that risperidone is probably twice as potent as haloperidol; therefore, maintenance dosages will generally range from 1 mg upwards, with individual dose titration as necessary. Many patients do well at 3 or 4 mg per day, and the use of 4 mg has been shown to be therapeutic in a European controlled trial. For older patients, even smaller dosages have been shown to be effective. Specific controlled studies in these patients have not yet been reported in the literature, but clinical reports of the use of doses lower than 1 mg being effective have led the manufacturer to try producing tablets smaller than 1 mg and a liquid preparation as well.

Risperidone has a half-life of 3 to 20 hours and is extensively metabolized to an active agent, 9-hydroxyrisperidone, which has a half-life of 21 to 30 hours. This metabolism takes place in the liver through the cytochrome P-450 IID6 isoenzyme system. This enzyme system is responsible for the metabolism of many neuroleptic and antidepressant agents, creating the possibility of important drug interactions. Isomorphism of this enzyme activity may explain the individual differences in metabolism. The majority of the drug's activity derives from the 9-hydroxy metabolite; yet, despite the long half-life of this metabolite, twice-a-day dosing is recommended by the manufacturer. This is apparently a Food and Drug Administration requirement despite the lack of any studies of once-a-day dosing. Drugs such as thioridazine, haloperidol, and loxapine are frequently used once a day at bedtime in routine clinical practice despite the lack of studies of once-a-day dosage. For the treatment of psychotic states, a starting dose of 1 mg twice a day should be used and the dosage increased slowly as the clinical state dictates, similar to the use of other antipsychotic agents. Converting from a typical neuroleptic to risperidone should not be done abruptly. It is also important not to discontinue anticholinergic drugs abruptly because this may lead to a worsening of extrapyramidal signs. If a patient is taking anticholinergic drugs, these should be continued and later withdrawn slowly after the transition to risperidone has taken place. Side effects with the use of risperidone include dizziness, sleepiness, and nausea, which, like extrapyramidal effects, are probably dose-related. Tachycardia and weight gain have also been reported.

Risperidone is expensive, costing as much as $2,000 per year per patient, but it offers an advantage over conventional neuroleptic agents in some patients, with about a 15% better response rate. It represents a distinct advance in therapeutics, particularly because it does not require blood monitoring, as does the use of clozapine. The exact place of risperidone in therapeutics is still to be determined. Many psychopharmacologists think that it should be a treatment of first choice in schizophrenia. Others suggest that patients should have an adequate trial of at least one typical neuroleptic agent, such as chlorpromazine or haloperidol, and if nonresponsive to this, then risperidone would be the next choice. The place of risperidone in the treatment of older patients or in affective disorders and other conditions where antipsychotic agents are used remains to be determined.

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REFERENCES

Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151:825-835

Owens DGC: Extrapyramidal side effects and tolerability of risperidone: A review. J Clin Psychiatry 1994; 55(suppl):29-35

Managing Agitated Patients in a General Hospital

AN AGITATED PATIENT in a general hospital setting is disruptive, dangerous, and usually in delirium. Agitated patients cause delays in patient recovery, increase patient and hospital costs, heighten family and staff anxiety, and can lead to patient and staff injury. Severely agitated patients show excessive physical activity and present a serious risk to themselves. Delirium is the most frequent cause of severe agitation in a general hospital, though mania, psychosis, dementia, and severe anxiety or depression can sometimes present with substantial agitation.

Delirium is a reversible impairment of cognition characterized by disorientation, impaired short-term memory, short attention span, altered perceptions of the environment, abnormal thought processes, inappropriate behavior, fluctuating levels of consciousness, and a worsening of symptoms at night. The last two symptoms are virtually diagnostic of delirium. Several factors usually contribute to delirium in patients, and a multifactorial cause should always be considered. Patients with dementia brain injury and older persons are particularly vulnerable to delirium.

The first priority in managing agitation due to delirium is to assess and treat the underlying cause. The immediate management of a patient's dangerous behavior usually requires additional intervention, however. Physical and chemical restraints can be effective in managing severe agitation and lowering the risk of injury to patients and staff. Mildly to moderately agitated patients who are responsive to verbal intervention can usually be managed with a multidisciplinary treatment plan that emphasizes physical and emotional supportive care, structured routines and activities, and the manipulation of environmental stimuli to help orient the patient and improve his or her coping mechanisms.

The cornerstone of chemical restraint for agitated patients is a high-potency neuroleptic agent. Haloperidol is most frequently used because of its ease of administration and titration and its reduced anticholinergic effect compared with other neuroleptics. The starting dose for acutely agitated patients can be from 1 to 10 mg, given by intravenous push, depending on the patient's age, size, and degree of agitation. Older patients should be started on lower doses of 1 to 3 mg. If the patient remains agitated, the starting dose should be doubled and readministered every 15 to 20 minutes until agitation is controlled. The patient should be closely monitored for adverse medication effects, including extrapyramidal symptoms, acute dystonia, akathisia, and the development of the neuroleptic malignant syndrome. Akathisia, a feeling of motor restlessness, is often mistaken for increased agitation. Most extrapyramidal symptoms respond to the use of antiparkinsonian agents, such as diphenhydramine, or to benzodiazepines.

Several other pharmacologic agents are used to control agitation. The use of benzodiazepines in combination with haloperidol is frequently helpful. Diazepam and lorazepam are easily administered and have a rapid onset of action. Lorazepam is used in patients with compromised liver function. Patients who are agitated during alcohol or sedative withdrawal can be managed with benzodiazepines alone. Aggressive management is recommended to prevent delirium tremens. Narcotic withdrawal and associated agitation should be managed with opioids. Patients who have been taking narcotics or benzodiazepines long term should be carefully tapered to prevent the development of agitation. Other psychotropic agents often used to control agitation and impulsivity include divalproex sodium, carbamazepine, propranolol, and buspirone.

Intensive care units are the most frequent setting for the occurrence of severe agitation because of the multiple stressors contributing to delirium and anxiety in patients. These include painful procedures or activities, environmental stimulation from constant noise and light, physical restraints, mechanical ventilation, and an unfamiliar environment. Frequently agitation occurs at the time a patient awakens from anesthetics, narcotics, and sedatives given at the time of admission or a surgical procedure. Inadequate pain control is a frequent contributor to agitation and must be carefully evaluated. A comprehensive treatment plan with good supportive care can minimize the need for physical and chemical restraints.

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REFERENCES

Fisher WA: Restraint and seclusion: A review of the literature. Am J Psychiatry 1994; 151:1584-1591

Kunik ME, Yudofsky SC, Silver JM, Hales RE: Pharmacologic approach to management of agitation associated with dementia. J Clin Psychiatry 1994; 55(suppl):13-17

Riker RR, Fraser GL, Cox PM: Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med 1994; 22:433-440

Diagnostic and Therapeutic Advances in Treatment-Resistant Mood Disorders

TREATMENT RESISTANCE poses a serious clinical dilemma for psychiatrists and may result in prolonged and serious consequences for patients, including death. When there is minimal response to treatment with antidepressant agents, psychotherapy, and supportive interventions and despite a trial of sufficient length, a systematic analysis becomes imperative to break through the stalemate.

Nearly a third of depressed patients (30%) fail to respond to conventional therapy, and as many as 60% have insufficient improvement of clinical indices at recovery. Obvious initial considerations involve a reassessment of the diagnosis (unipolar, bipolar, atypical, rapid cycling, seasonal), medication dosage, patient compliance with treatment, and the presence of comorbid psychiatric and medical disorders (including substance abuse, cognitive disorders, and endocrine and oncologic disorders).

Although brain imaging procedures are not definitive diagnostic or predictive tools for treatment resistance, they have great promise for understanding structural and neurochemical abnormalities that may define a treatment plan for specific patients. For example, one study using hexamethylpropylene amine oxime and single-photon-emitted computed tomography has implied that the limbic system plays an important role in mediating treatment refractoriness.

Gender, genetic, and age characteristics may contribute to mood disorder subtypes (psychosis, catatonia, pseudodementia, and severe vegetative signs) requiring specific intervention. Special pharmacokinetic issues such as medication absorption, interaction, and plasma drug concentration should be considered because there

can be as much as a 30-fold range of drug metabolic differences among patients.

Numerous augmentation strategies have been proposed to combine antidepressant agents with the following categories of drugs:

- Mood-stabilizing agents: lithium, anticonvulsants (valproic acid, carbamazepine, lamotrigine); calcium channel blockers: verapamil, nimodipine, isradipine.
- Receptor agonist-antagonists: buspirone, pindolol.
- Neurotransmitter enhancement: fenfluramine, norepinephrine serotonin reuptake inhibitors (venlafaxine, nefazodone); tricyclic antidepressants: selective serotonin reuptake inhibitors, monoamine oxidase inhibitors.
- Thyroid hormone.

The dose level and length of trial augmentation may be crucial variables in determining the therapeutic effect. When using thyroid augmentation, a baseline thyroid assessment should be made—including extrasensitive thyroid-stimulating hormone (TSH; thyrotropin) and thyrotropin-releasing hormone when indicated. The administration of triiodothyronine may be more effective than thyroxine for augmentation, but caution should be exercised to avoid inducing hypothyroidism.

Innovative treatment approaches to augmentation using unique neurobiologic pathways include cortisol synthesis inhibitors: ketoconazole and metyrapone; selective and reversible monoamine oxidase agents: selegiline and moclobemide; and serotonin-dopamine blocking agents: clozapine.

Electroconvulsive treatment remains a solid alternative both in the sequence of treatment decisions and for primary intervention in selected cases of severe suicidal potential or deteriorating physical health demanding a rapid reversal. More recent innovative approaches through brain area-specific electromagnetic radiation may hold promise in patients with the most severely resistant disorders.

Special psychosocial and trauma-inducing factors may influence the course of affective illness, including bereavement, loss and separation, status devaluation, learned helplessness, immigration and displacement, and natural disaster. The neurobiologic response characteristics of psychological stress and trauma may augment, prolong, and have a deteriorating effect on a mood disorder. With the chronicity of illness, actual central nervous system structural damage and problematic kindling of mood disregulation may lead to a further deterioration.

Thoughtful analysis and vigorous response to treatment-resistant mood disorders are imperative to bring about clinical improvement and to establish a firm groundwork for the most crucial phase of treatment to come—preventing relapse.

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REFERENCES

Ebert D, Albert R, May A, et al: Combined SSRI-RIMA treatment in refractory depression—Safety data and efficacy. Psychopharmacology 1995; 119:342-344

Ghadirian AM, Engelsmann F, Dhar V, et al: The psychotropic effects of inhibitors of steroid biosynthesis in depressed patients refractory to treatment. Biol Psychiatry 1995; 37:369-375

Nolan W, Zohar J, Roose S, et al: Refractory Depression. New York, NY, John Wiley & Sons, 1994

Sunderland T, Cohen RM, Molchan S, et al: High-dose selegiline in treatment-resistant older depressive patients. Arch Gen Psychiatry 1994; 51:607-615

Vanelle JM, Loo H, Galinowski A, et al: Maintenance ECT in intractable manic-depressive disorders. Convuls Ther 1994; 10:195-205

Adult Attention-Deficit Disorder

ATTENTION-DEFICIT HYPERACTIVE DISORDER is most likely a group of conditions. Family-genetic data identify four subtypes: attention-deficit hyperactive disorder plus either conduct, mood, anxiety, or learning disorders. These subtypes may have differing risk factors, clinical courses, and pharmacologic responses.

The diagnosis of adult attention-deficit disorder requires that a patient meet several criteria: either inattention or hyperactivity persisting from childhood and three of the following: inability to complete tasks, impaired interpersonal relationships or inability to sustain relationships over time, hot or explosive temper, and stress intolerance. Additional characteristics include difficulty in directing and sustaining attention, being easily overwhelmed by tasks of daily living, difficulty in maintaining an organized living or work place, inconsistent work performance, inattention to detail, making decisions without anticipating consequences, difficulty delaying gratification, stimulation seeking, restlessness, low frustration tolerance, and impatience. Adults who previously qualified for attention-deficit disorder of childhood show a 10% to 50% persistence of core symptoms of inattention, impulsivity, and hyperactivity.

Women with this disorder have higher rates of depression, anxiety, and oppositional disorders and more evidence of school failure and cognitive impairment than female controls. The pattern of psychopathology, impaired cognition, and psychosocial functioning is similar to that in affected men with the disorder, except for a lower incidence of comorbid conduct disorder in women.

The psychiatric comorbidity of adult attention-deficit hyperactive disorder parallels that in children, the most common comorbid conditions being affective disorders, Tourette's syndrome, and anxiety, conduct, and learning disorders.

The incidence of comorbidity with affective (mood) disorders ranges from 15% to much higher, depending on the sample. Elevated rates of major depressive disorder, including bipolar disorder, have been found in first-degree relatives of patients with attention-deficit hyperactive disorder. Accordingly, assessment should include not only symptoms of attention-deficit hyperactivity, but also a mood history and a detailed family psychiatric history. The response to stimulants for patients with attention-deficit hyperactivity plus major depressive disorder may be poor, and if antidepressants are used alone, manic switching may occur. Pharmacotherapy with multiple agents may be needed, including a stimulant, a mood stabilizer, and an antidepressant.

Attention-deficit hyperactive disorder with conduct disorder in adolescents and in adults with antisocial personality disorder often coexists with substance abuse disorder. Long-term outcome studies of grown-up children with the disorder show 15% to 40% lifetime rates of drug abuse, which may contribute to and confound assessment of the cognitive disability. It is possible in some cases that comorbidity emerges as an attempt at self-medication.

Several studies indicate a 60% beneficial response to the use of psychostimulants alone. Clonidine and guanfacine, α_2-noradrenergic agonists, have been used to decrease aggression and impulsivity. Nonpharmacologic treatment modalities include psychotherapy, teaching time management, family systems approaches, problem solving, communication training, and learning modification, if a learning disability is present. When a comorbid diagnosis of substance abuse is present, nonpharmacologic treatment may be preferable, including group therapy, individual treatment of substance use disorder and group homes, or residential treatment when indicated.

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REFERENCES

Biederman J, Faraone SV, Spencer T, et al: Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 1993; 150:1792-1798

Murphy K, Borkley RA: Preliminary normative data on DSM-IV criteria for adults. ADHD Rep 1995; 3:6-7

Murphy K, Lellert S: Out of the Fog: Treatment Options and Coping Strategies for Adult Attention Deficit Disorder. New York, NY, Hyperion, 1995

Behavioral Genetics

THE APPLICATION OF molecular genetic technology to the study of psychiatric and behavioral disorders has led to a plethora of exciting but often unreplicated findings. Difficulties in the analysis of complex traits and diseases that do not follow simple mendelian patterns are receiving increasing attention but have not deterred the premature acceptance of the validity of reports regarding animals and humans. A mutant mouse model involving a genetic disruption of nitric oxide synthase has been linked to human aggression, and other mouse loci have been related to "anxiety or neuroticism" and to alcohol and morphine dependence. Studies in humans have suggested a link between male homosexuality and a region (q28) on the X chromosome, between attention-deficit hyperactivity and reading disability and a locus on chromosome 6, and between aggression and sociopathy and a point mutation in the structural gene for monoamine oxidase A. Recent studies have indicated that "novelty seeking" in humans may be related to the D_4 dopamine-receptor gene. At least a half dozen loci have been implicated as contributing to schizophrenia, the most recent being a gene on chromosome 6. None of these have received convincing independent replication, however, including the previous "hot" finding linking a band on the long arm of chromosome 5 to schizophrenia.

The story is similar for manic-depressive illness, where recent linkages between the disorder and loci on the short arm of chromosome 18 or the long arm of chromosome 21 are isolated findings marked by increasing skepticism. Whereas there is agreement of a strong genetic contribution to major psychiatric illnesses and to variables of normal human temperament, it has become clear that behavioral phenotypes are exceedingly difficult to determine and that falsely positive determinations of affected status (phenocopies) are extremely harmful to linkage analyses. Until replicated, reports of specific genetic linkage to given psychiatric disorders should be viewed with caution; patients and their families may experience disillusionment when such apparent advances in diagnosis and, potentially, in new therapeutic interventions prove to be illusory.

The genetic heterogeneity of behavioral disorders has underscored the need to supplement traditional familial linkage methods with sib-pair analyses and population-based association studies in appropriate study groups, most ideally those in which a "founder effect" is probable, such as the Finnish, Amish, and French-Canadian populations. When reproducible genetic linkage studies emerge, it is likely that environmental factors will be found to play a major role in the degree to which a given vulnerability gene(s) is expressed. As yet, however, the promise of psychiatric genetics is unfulfilled, and caution is warranted until appropriate methodologic practice is followed.

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REFERENCES

Cardon LR, Smith SD, Fulker DW, Kimberling WJ, Pennington BF, DeFries JC: Quantitative trait locus for reading disability on chromosome 6. Science 1994; 226:276-279

Ebstein RP, Novick O, Umansky R, et al: Dopamine D_4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. Nature Genet 1996; 12:78-80

Flint J, Corley R, DeFries JC, et al: A simple genetic basis for a complex psychological trait in laboratory mice. Science 1996; 269:1432-1435

Kelner K, Benditt J (Eds): Genetics and behavior. Science 1994; 264: 1696-1739

Moises H, Yang L, Kristbjarnarson H, et al: An international two-stage genome-wide search for schizophrenia susceptibility genes. Nature Genet 1995; 11:321-324

Nelson RJ, Demas GE, Huang PL, et al: Behavioural abnormalities in male mice lacking neuronal nitric oxide synthase. Nature 1996; 378:383-386

Straub RE, Lehner T, Luo Y, et al: A possible vulnerability locus for bipolar affective disorder on chromosome 21q22.3. Nature Genet 1994; 8:291-295

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Alerts, Notices, and Case Reports

Hypoglycemia Associated With the Use of Fluoxetine

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HYPOGLYCEMIA HAS many causes in patients who do not have diabetes mellitus, in contrast to patients with diabetes mellitus, in whom hypoglycemia is most often due to the use of insulin or oral hypoglycemic agents. We report a case of symptomatic hypoglycemia associated with fluoxetine use in a patient with non–insulin-dependent diabetes mellitus. Symptoms of sweating, tremor, or anxiety occur in 10% or more of patients taking fluoxetine[1,2] and can easily be confused with hypoglycemia that occurs in diabetic patients.[3] In the case reported here, symptomatic hypoglycemia was associated with increased blood insulin levels during a 72-hour fast while the patient was taking fluoxetine. This case emphasizes the importance in evaluating the occurrence of hypoglycemia of discontinuing all nonessential medications during a 72-hour fast.

Report of a Case

The patient, a 53-year-old man diagnosed with non–insulin-dependent diabetes mellitus six years before admission, was treated with glyburide, 20 mg per day. Four months before admission, treatment with fluoxetine, 20 mg per day, was started for depression. The patient began having episodes of confusion, fatigue, dry mouth, and blurred vision. During some of these episodes, his blood glucose level was reportedly as low as 2.36 mmol per liter (43 mg per dl) as determined by self-monitoring. These episodes occurred paroxysmally, but his symptoms were relieved with food. A trial of discontinuing the glyburide was attempted, but his symptoms continued. In addition, while taking fluoxetine, the patient lost 13 kg (29 lb).

The patient was admitted to an outside hospital for a 72-hour fast to evaluate his hypoglycemia. He had stopped taking glyburide two weeks before admission but continued taking fluoxetine during the fast. During the second and third days of the fast, episodes of symptomatic hypoglycemia were noted. One episode occurred about 48 hours into the fast, with a blood glucose level of 2.1 mmol per liter (normal, 4.2 to 6.4) and a simultaneous serum insulin level of 129 pmol per liter (18 μU per ml; normal, 35 to 145 pmol per liter). A second episode occurred after 60 hours of fasting, with a blood glucose level of 2.4 mmol per liter, a serum insulin level of 237 pmol per liter, and a C-peptide value of 4.1 μg per liter (normal, 0.5 to 2.0). Insulin and C-peptide levels were determined by radioimmunoassay (Diagnostic Products Corporation). A urine specimen collected during the fast was negative for sulfonylureas as determined by high-performance liquid chromatography using an ultraviolet light detector (National Medical Services, Inc). Thyroid, liver, and renal function test results were normal, and anti-insulin antibodies were absent. An abdominal computed tomographic scan showed no pancreatic abnormality. Esophagogastroduodenoscopy and endoscopic ultrasonography revealed mild heterogeneity of the pancreatic head. The patient was referred to the University of Washington School of Medicine (Seattle) for further evaluation of an insulinoma.

The patient was admitted two months later for a second 72-hour fast. Glyburide had not been used between the fasts, and fluoxetine was discontinued 24 hours before the second fast. During the second fast, no hypoglycemic symptoms were noted. Blood glucose levels ranged from 3.8 to 7.8 mmol per liter, with serum insulin concentrations of 43 to 108 pmol per liter. No further testing was done, and the patient was discharged.

Hyperglycemia later developed, and glyburide therapy was reinstituted at a lower dose. At the discretion of the practicing physician, the use of fluoxetine was continued for depression. The patient continued to have episodes of hypoglycemia, albeit less severe.

Discussion

Hypoglycemic symptoms result from the release of counterregulatory hormones and neuroglycopenia. As blood glucose levels begin to decrease, the initial symptoms of hypoglycemia, including tremors, diaphoresis, and palpitations, occur from the release of epinephrine. Neuroglycopenic symptoms of lethargy, confusion, and loss of consciousness occur with further decreases in the blood glucose concentration. Causes of hypoglycemia include drugs, excess insulin production—insulinoma—anti-insulin antibodies, and concomitant diseases that may compromise glucose production.

In evaluating hypoglycemic symptoms, the documentation of hypoglycemia (<2.2 mmol per liter) at the time of symptoms is required (one of the diagnostic criteria in Whipple's triad[4]). Occasionally this can be accomplished on an outpatient basis, but the standard protocol is a 72-hour fast with frequent taking of blood specimens to correlate symptoms with glucose, insulin, and C-peptide levels.[5] Insulin-mediated hypoglycemia is associated with an inappropriately elevated insulin level (>43 pmol per liter) at the time of hypoglycemia. Other pancreatic islet β-cell peptides can be used to differentiate between the various insulin-mediated hypoglycemias.[5]

In the case reported here, the hypoglycemia was clearly associated with symptoms and, by history, relieved with food. The elevated serum insulin and C-

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peptide concentrations during the first 72-hour fast are consistent with an endogenous insulin-mediated hypoglycemia. Oral hypoglycemic agent use seems unlikely because sulfonylureas were absent in the urine. These laboratory results mimic those expected for an insulinoma. When fluoxetine was discontinued before the second 72-hour fast, however, no hypoglycemia was noted, suggesting that fluoxetine use during the first 72-hour fast contributed to the disorder.

It is unclear whether fluoxetine use per se induced the hypoglycemia or if it potentiated a glyburide-induced hypoglycemia. Hypoglycemia from sulfonylureas can occur 48 to 72 hours after the last dose.[6] Because by history the patient discontinued glyburide use two weeks before fasting, glyburide-induced hypoglycemia seems unlikely. The absence of sulfonylureas in the urine is consistent with this conclusion, but sulfonylurea use during the fast cannot be entirely discounted because assays for sulfonylureas may not have the sensitivity for low levels of second-generation sulfonylureas and their metabolites.[7]

Many drugs have been shown to potentiate the hypoglycemic effects of sulfonylureas by altering either the pharmacokinetics of sulfonylurea metabolism or pharmacodynamic interactions.[6] Pharmacokinetic data suggest that with multiple dosing of glyburide, the drug equilibrates with a slowly turning over compartment, possibly adipose tissue.[8] It is conceivable that fluoxetine use potentiated the hypoglycemic effect of glyburide by displacing glyburide from this compartment. Discontinuing glyburide 14 days before the fast would seem to rule out this possibility because the slowly turning over compartment would have to have a half-life of more than three days.

Numerous drugs can induce hypoglycemic symptoms with or without hypoglycemia. The side-effect profile of fluoxetine overlaps with hypoglycemia, and this appears to be a common property of selective serotonin-reuptake inhibitors. In this case, however, hypoglycemic symptoms associated with the use of fluoxetine appeared to be caused by a low-blood glucose level. A poorly documented case of symptomatic hypoglycemia associated with fluoxetine use has been reported elsewhere.[9]

Fluoxetine has been used to treat obese patients with non–insulin-dependent diabetes to induce weight loss.[10,11] These studies noted an improvement in glycemic control with the administration of fluoxetine, 60 mg per day, as manifested by a decrease in hemoglobin A_{1C} levels in conjunction with a decrease in caloric intake and an average weight loss of 4 to 6 kg (9 to 13 lb). No episodes of hypoglycemia were reported in these studies. The improvement in glycemic control in these studies is likely due to weight loss. The weight loss this patient experienced likely accounted for the improved glycemic control, allowing the discontinuation of glyburide before and the normal glucose levels during the second fast, but it would not account for the hypoglycemia. In addition, fluoxetine has been shown to improve peripheral insulin action and decrease hepatic glucose production in insulin-resistant patients.[12]

In prescribing selective serotonin-reuptake inhibitors to diabetic patients, the American Hospital Formulary Service recommends careful monitoring of blood glucose levels in all patients with diabetes initiating or discontinuing these agents.[13] This seems practical advice concerning the use of this class of agents in these patients, especially those on concomitant sulfonylurea therapy, as illustrated in this case. We also recommend that in evaluating hypoglycemic symptoms in patients taking selective serotonin-reuptake inhibitors, stopping the medication should be an initial diagnostic maneuver. This case also emphasizes that in evaluating hypoglycemia, all nonessential medications should be stopped during the 72-hour fast.

REFERENCES

1. Wernicke JF: The side effect profile and safety of fluoxetine. J Clin Psychiatry 1985; 46(pt 2):59-67
2. Cooper GL: The safety of fluoxetine—An update. Br J Psychiatry 1988; 153(suppl 3):77-86
3. Lear J, Burden AC: Fluoxetine side-effects mimicking hypoglycaemia (Letter). Lancet 1992; 339:1296
4. Whipple AO: The surgical therapy of hyperinsulinism. J Int Chir 1938; 3:237-276
5. Service FJ: Hypoglycemic disorders. N Engl J Med 1995; 332:1144-1152
6. Jackson JE, Bressler R: Clinical pharmacology of sulphonylurea hypoglycaemic agents: Part 2. Drugs 1981; 22:295-320
7. Rogers HJ, Spector RG, Morrison PJ, Bradbrook ID: Pharmacokinetics of intravenous glibenclamide investigated by a high performance liquid chromatographic assay. Diabetologia 1982; 23:37-40
8. Balant L, Zahnd GR, Weber F, Fabre J: Behaviour of glibenclamide on repeated administration to diabetic patients. Eur J Clin Pharmacol 1977; 11:19-25
9. Katz LM, Fochtmann LJ, Pato MT: Clomipramine, fluoxetine, and glucose control. Ann Clin Psychiatry 1991; 3:271-274
10. O'Kane M, Wiles PG, Wales JK: Fluoxetine in the treatment of obese type 2 diabetic patients. Diabet Med 1994; 11:105-110
11. Gray DS, Fujioka K, Devine W, Bray GA: Fluoxetine treatment of the obese diabetic. Int J Obes 1992; 16:193-198
12. Potter van Loon BJ, Radder JK, Frölich M, Krans HMJ, Zwinderman AH, Meinders AE: Fluoxetine increases insulin action in obese nondiabetic and in obese non-insulin-dependent diabetic individuals. Int J Obes 1992; 16:79-85
13. McEvoy GK (Ed): American Hospital Formulary Service 1995: Drug Information. Bethesda, Md, American Society of Health-System Pharmacists, 1995, pp 1483-1495

Conflict of Ethics and Practice in Hospitalized Patients Who Want to Smoke

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THE MEDICAL PROFESSION views smoking as a major health hazard and encourages physicians to help patients

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stop smoking.[1,2] Many hospitals have nonsmoking policies and may even sponsor smoking-cessation campaigns.[3-5] Some variations do exist, however, in how hospitals and health care institutions deal with patients who smoke. Patients in psychiatric units, for example, may be allowed to smoke in a supervised setting outside the hospital to moderate disruptive behavior.[6] Disabled patients in rehabilitation settings may be wheeled outside by hospital staff so that they may be able to smoke. In this report, we describe a conflict involving a disabled patient admitted to a hospital who insisted on smoking against hospital policy.

Report of a Case

The patient, a 38-year-old man, was admitted to a community teaching hospital because of a large sacral decubitus ulcer. Eight years before admission, he sustained a gunshot wound to the thoracic spine, with resultant paraplegia. At that time, he also underwent a colostomy and ileostomy because of the gunshot wound. A large sacral decubitus subsequently developed that resulted in several admissions to local hospitals.

The patient lived in a group home for independent living. He had had paranoid schizophrenia since age 18 and was being maintained on a regimen of fluphenazine hydrochloride. In the group home, he received daily wound and colostomy care by a visiting nurse. Just before this admission, the patient was admitted to another hospital because of increasing drainage from his sacral decubitus. Within a few days, he signed out against medical advice and returned to his group home. Because the visiting nurse association was unaware that the patient was leaving the hospital, no plans were made to reinstitute care. After three days at home, the patient presented to a community hospital by ambulance to obtain wound and colostomy care. On admission his medications included fluphenazine, multiple vitamins, and a diuretic. He smoked one pack of cigarettes per day and drank three to four 12-ounce cans of beer per day.

The patient was hypothermic at 35.5°C (96°F) and appeared cachectic. His affect was angry, disgruntled, and agitated. He was generally uncooperative with the history taking and physical examination. His blood pressure was 110/70 mm of mercury, with a heart rate of 128 beats per minute and a respiratory rate of 24. He had poor dentition. His abdomen showed a functioning left colostomy and right ileostomy. He had 4+ lower extremity edema with ulcer formation on his right shin and both feet. The patient had a massive 30- by 30-cm grade IV decubitus ulcer of the sacrum extending to the lumbar spine and the sacroiliac region. Below the level of T-10, he was paralyzed and insensate.

Pertinent laboratory data included a hemoglobin level of 68 grams per liter (6.8 grams per dl), with a normal leukocyte count. The admission sodium level was 125 mmol per liter; the remaining electrolyte, urea nitrogen, and glucose levels were normal.

The patient was admitted to the hospital for wound care and the management of associated problems. Once admitted, he posed a challenging care dilemma. He wanted to smoke, something that was not permitted in this hospital. When told he was not allowed to smoke, the patient became verbally abusive and refused colostomy care and wound care in an attempt to force the nursing staff to allow him to smoke. Attempts to control his smoking were unsuccessful. When he could, the patient would smoke until it was detected by patients or staff. When his cigarettes were confiscated, he paid a delivery person or asked friends to bring him cigarettes. In addition, the patient's smoking resulted in requests by other patients to smoke and complaints from other patients and staff about the smoke.

Although all the members of the patient care team knew that smoking was prohibited, they did not agree about how to deal with this patient. Some argued that visitors, staff, and even ambulatory patients who wanted to smoke could do so by going outside. Because the patient was paraplegic, debilitated, and completely immobile, he was not able to do so. There was empathy with the patient's frustration at being refused one of the few activities that gave him pleasure. The nurse floor manager also felt that the demands on personnel time were increased by having to deal with policing the patient and the repercussions of not allowing him to smoke. The argument against allowing the patient to smoke involved the institutional policy against smoking and the effect of secondhand smoke on the staff and on other patients. In addition, there were concerns about the deleterious effects of smoking on his wound healing.

The nurse manager's solution, which was approved by the hospital's risk management department, was to allow the patient to smoke in his room supervised by a nurse or aide. This meant that his cigarettes (and matches) were kept in the nurses' station at all times. Every time he would smoke, a staff member would light his cigarette and supervise him until he was done. If there were any complaints about the smoking, the staff person was instructed to extinguish the cigarette.

Over the course of the week, the patient's medical condition improved to where he was able to use a prone cart to transport himself. With the use of the prone cart, he was able to wheel himself off the floor and outside to the designated smoking areas. His smoking on the floor ceased, and the remainder of his hospital course was uneventful.

Discussion

Several concerns arise with how this case was resolved. In a competent patient, refusal of care need not involve manipulation. If a patient is considered capable of making decisions, the staff should not attempt to provide unwanted care, namely wound and colostomy care. Although this patient elected to come to the hospital in the first place and can be presumed to have wanted medical attention, he may no longer have wanted it. After a discussion of the risks of refusing care, if the patient no longer wanted to receive care, he should have been discharged from the hospital. If, however, he was not consid-

ered capable of making decisions, his right to refuse care needed to be reexamined and an alternative identified. Forcing unwanted care on anyone is not desirable. The use of alternatives that can support a patient through nicotine withdrawal, such as nicotine patches and clonidine and tranquilizers for autonomic symptoms, must be considered. Consent is still needed to institute any of these options. Unfortunately, instead of dealing directly with the patient's decision-making capacity and implications for treatment choices, the staff became enmeshed in the primary goal of wanting to provide care, perceived to be in the patient's best interest, and acquiesced to the patient's request to smoke in order to do so.

This case can be analyzed in terms of accepted principles of medical ethics.[7(p277)] The argument can be advanced that respect for autonomy means that a competent person may choose high-risk or unhealthy behaviors. Smoking is not unique in this regard. Patients with diabetes mellitus may decide to eat chocolate bars. Patients with hypertension may stash and eat salted snack foods. To forbid a competent patient to smoke is paternalistic—that is, acting for a patient's good contrary to that patient's wishes. Some behaviors, generally those involving the use of addictive substances, are intuitively viewed differently. Should a patient with alcoholism be permitted to drink while in a hospital? Should a patient who uses illegal drugs be permitted to use them in a hospital? Whereas respect for autonomy supports a person's right to refuse recommended treatment and even to make "bad choices," certain behaviors and thus claims to autonomy may be limited by rules of an institution.

The autonomy issue sags even if it does not collapse with questions about a patient's decision-making capacity. Although capacity or competence is to be presumed for persons entering a hospital, the competence of this patient, who had a complicated psychiatric and social history, requires confirmation. If the patient ultimately is found to lack decision-making capacity, acting in his best interest is morally sound. This would be considered weak paternalism, a reasonable ethical practice.[8] In weak paternalism, an agent intervenes on grounds of beneficence or nonmaleficence only to prevent substantially nonvoluntary conduct to protect persons against their own substantially nonautonomous action(s). Substantially nonvoluntary or nonautonomous actions include cases of inadequately informed consent, severe depression that precludes rational deliberation, and severe addiction that prevents free choice and action. Weak paternalism requires that some such form of compromised ability be present.[7] Does the patient's exercise of autonomy include adequate reflection on the consequences of his or her act?[9] Those consequences could be on the patient. They could also affect the community, the community in this case being a hospital, whose services the patient has presumably sought. In accepting care in the hospital, the patient implicitly consented to abide by the institutional policies, which could include the prohibition of smoking.

Some other ethical principle is required to adequately address this issue. Beneficence alone cannot resolve the question. Medical beneficence implies serving the patient's best interest. In this case, a conflict existed between the patient's and the caregivers' views about what constituted those best interests. The patient's idea of a good—that is, satisfying his addictive craving—conflicted with the medical view of "good": abstaining from smoking and healing of his decubitus ulcers. It could be argued that by permitting the patient to smoke, we gained his cooperation with other aspects of his medical regimen and thereby facilitated a good medical outcome. This is consistent with the practice of allowing psychiatric patients to smoke in their units with supervision, with the anticipated outcome being lessening of their underlying psychiatric disorder.

Community interest, along with serving the interests the patient may or may not want, may bring us closer to a proper resolution of the dispute. In purely utilitarian terms, the medical benefit to the patient along with benefits to other patients and hospital employees, possibly inconvenienced, discomforted, or endangered, makes refusing the patient's wish a reasonable course of action. It has been argued that "An action may be said to be conformable to the principle of utility when the tendency it has to augment the happiness of the community is greater than any it has to diminish it."[10(p66)]

The language of rights is insufficient. No right to smoke exists. As a practical matter, the patient would have a roommate, and that roommate's right not to be exposed to smoke seems to have precedence similar to a right not to be harassed by loud television or radio playing.

Justice, including the protection of other patients who will be endangered by a patient's smoking, exerts a claim. Despite a patient's claim of autonomy, the danger of passive smoke exposure, the discomfort therefrom, and the greater claims on finite resources, such as the required supervision by nurses for the patient's smoking, seem to have priority over a patient's claim to autonomy. Smoking is an obstacle to the healing of a decubitus ulcer in the presence of circulatory compromise. The patient's unwillingness to comply with a medically necessary course of action at a minimum strained his claim to entitlement to ongoing care if the efficacy of that care was undermined by continued smoking.[11]

Promise keeping is another principle, described as a nonconsequentialist principle having priority over beneficence.[12] A professional promise of physicians, nurses, and hospitals is to seek the healing and wholeness of patients. Denying consent to a patient to smoke or not providing the facilities in which to smoke (a private supervised environment) is completely consistent with honoring the promise of seeking the healing of the patient. Simply because a competent patient may elect to release a professional from the terms of that promise does not negate its general nature. Professionals as moral agents understandably wish to honor the promises intrinsic to their practice.

As a practical matter, patients have other options. If competent, they can choose to satisfy a craving over the

good of healing and try to find a physician or hospital that would allow them to smoke. If their wishes are sufficiently compelling, they might to able to be transferred to such a facility. Patients can also be pharmacologically supported through their nicotine withdrawal. Nonetheless, respect for autonomy would on balance seem to be exceeded by the requirement of justice—that is, a fair distribution of benefits and burdens (right to smoke versus the right to be protected from smoke and the fair allocation of scarce resources, personnel, and space needed to supervise smoking)—and the promise keeping whereby the hospital, nurses, and physicians honor their promise to promote health and wholeness.

Conclusion

This case illustrates the difficulties of reconciling what appears on the surface to be a clear-cut problem of the rules of a smoke-free hospital conflicting with the realities of daily practice. Supervised smoking in a hospital violates institutional policies. If we allowed the patient in this case to smoke in the hospital, we would have respect of autonomy disproportionately outweighing important principles such as justice and promise keeping. Demands on clinicians can make an ad hoc solution more attractive than enforcing an institutional rule or attending to the community of patients. More data are needed to understand how clinicians resolve problems involving institutional requirements and limits to patient autonomy. Finally, this case invites further study of the mutual interests of hospitals as social institutions and patients and caregivers as community.

REFERENCES

1. Fiore MC, Epps RP, Manley MW: A missed opportunity—Teaching medical students to help their patients successfully quit smoking. JAMA 1994; 271:624-626

2. Kaufman NJ: Smoking and young women—The physician's role in stopping an equal opportunity killer. JAMA 1994; 271:629-630

3. Goldstein AO, Westbrook WR, Howell RE, Fischer PM: Hospital efforts in smoking control: Remaining barriers and challenges. J Fam Pract 1992; 34: 729-734

4. Stevens VJ, Glasgow RE, Hollis JF, Lichtenstein E, Vogt TM: A smoking-cessation intervention for hospital patients. Med Care 1993; 31:65-72

5. Hospital smoking bans may help patients quit. Am J Nurs 1994; 94:13

6. Taylor NE, Rosenthal RN, Chabus B, et al: The feasibility of smoking bans on psychiatric units. Gen Hosp Psychiatry 1993; 15:36-40

7. Beauchamp TL, Childress FJ: Principles of Biomedical Ethics, 4th edition. New York, NY, Oxford University Press, 1994

8. Feinberg J: Legal paternalism. Can J Philos 1971; 105:24

9. Miller BL: Autonomy and the refusal of lifesaving treatment. Hastings Center Rep 1981; 11:24-28

10. Bentham J: An introduction to the principles of morals and legislation. *In* Ryan A (Ed): Utilitarianism and Other Essays. London, Penguin Books, 1987

11. Ainsworth MA, Hogan DL, Koss MA, Isenberg JI: Cigarette smoking inhibits acid-stimulated duodenal mucosal bicarbonate secretion. Ann Intern Med 1993; 119:882-886

12. Veatch RM: Resolving conflicts among principles: Ranking, balancing, and specifying. Kennedy Inst Ethics J 1995; 5:199-218

Diffuse Infiltrative Lymphocytosis Syndrome in a Patient Not Infected With the Human Immunodeficiency Virus

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DIFFUSE INFILTRATIVE LYMPHOCYTOSIS syndrome is an immunologic disorder associated with the major histocompatibility complex (MHC) gene locus *HLA-DR5*.[1,2] In patients with this disorder, there is diffuse infiltration of the salivary glands, lungs, gastrointestinal tract, and breast tissue by CD8 T cells. The disorder clinically resembles Sjögren's syndrome, but differs in the extent of extraglandular involvement, paucity of autoantibodies, and association with *HLA-DR5*, all of which are found in diffuse infiltrative lymphocytosis.[3,4(p145),5] In contrast, in patients with Sjögren's syndrome, CD4 T lymphocytes infiltrate the salivary and lacrimal glands, and extraglandular manifestations are present only a third of the time; high titers of autoantibodies to extractable nuclear and cytoplasmic antigens (Ro/SSA and La/SSB) are frequently present. Sjögren's syndrome is associated with *HLA-DR2* and *HLA-DR3*.[6]

Cases of diffuse infiltrative lymphocytosis syndrome have been described in the literature as disseminated lymphocytic infiltrative process[7,8] or intestinal pneumonitis[9] and have occurred in patients infected with the human immunodeficiency virus (HIV). We describe a case of diffuse infiltrative lymphocytosis syndrome in a patient not infected with HIV.

Report of a Case

The patient, a 53-year-old man, presented to his physician in June 1993 with a swollen left submandibular mass. Other than a 15-pack-year history of smoking, his medical history was unremarkable. He had no arthritic complaints, rash, cough, or constitutional symptoms. He did not have dry eyes or xerostomia. There was no history of exposure to tuberculosis, but the patient had received the bacille Calmette-Guérin vaccine previously in China. Biopsy of the submandibular mass revealed chronic sialoadenitis of the salivary gland, and tests were negative for acid-fast organ-

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CT = computed tomographic
HIV = human immunodeficiency virus
HTLV-I = human T-cell lymphotropic virus type I
MHC = major histocompatibility complex

isms. A chest roentgenogram revealed diffuse pulmonary fibrosis in the bases bilaterally without mediastinal adenopathy. The patient was found to be positive on a tuberculin (purified protein derivative) test, but smears and subsequent cultures were negative for tuberculosis.

In August 1993, further evaluation found the patient to test negative for HIV, human T-cell lymphotropic virus type 1 (HTLV-I), Ro/SSA, La/SSB, hepatitis C, syphilis, and hepatitis B surface antigen; tests for antinuclear antibodies, rheumatoid factor, and angiotensin-converting enzyme (ACE) inhibitor were negative. The patient was positive for hepatitis B core antibody (immunoglobulin G), but liver function test results were normal.

The patient continued to do well until November 1993, when he presented with a two-week history of jaundice, anorexia, and fatigue. At this time, his liver function test values were grossly abnormal, with a total bilirubin level of 100 μmol per liter (5.9 mg per dl); alkaline phosphatase, 604 U per liter; aspartate aminotransferase (AST, formerly SGOT), 220 U per liter; alanine aminotransferase (ALT, formerly SGPT), 438 U per liter; and lactate dehydrogenase, 242 U per liter. An abdominal computed tomographic (CT) scan revealed a diffusely enlarged pancreas with extension to the left kidney, a dilated gallbladder, and an enlarged common bile duct with evidence of obstruction in the head of the pancreas. A benign-appearing nodule was also noted in the left lower lobe of the lung. After an endoscopic retrograde cholangiopancreatogram was unsuccessful, a stent was placed percutaneously from the hepatic portal to the junction of the third and fourth portions of the duodenum. Biopsy of the head of the pancreas revealed diffuse lymphocytic infiltration without evidence of malignancy. Following the stent placement, the patient's liver function test values returned to normal except for a persistently elevated alkaline phosphatase level, and he was able to return to work. Four months later, in March 1994, another abdominal CT scan revealed an enlarged but stable pancreas, persistent left kidney infiltrate, and slight degeneration of the liver. The previously noted nodule in the left lower lobe of the lung was also unchanged.

The patient did well until July 1994 when he presented to his private physician with right upper quadrant pain, jaundice, and fever to 39.4°C (103°F). He was found to have leukocytosis with a leftward shift, elevated aminotransferase levels (AST, 75 U per liter; ALT, 107 U per liter), total bilirubin level (116 μmol per liter [6.8 mg per dl]), and an alkaline phosphatase value of 1,168 U per liter. The patient was treated for presumptive cholangitis with the administration of piperacillin sodium and metronidazole; he rapidly improved. Another CT scan of the abdomen was unchanged compared with the study of March 1994. A second percutaneous drainage of the biliary obstruction was done, and a new stent was placed. A small mass in the common bile duct was now also noted. Biopsies of the biliary mass, head of the pancreas, kidney, and the nodule at the lung base all revealed diffuse lymphocytic infiltration with no signs of malignancy or vasculitis. Retesting was again negative for HIV, HTLV-I, rheumatoid factor, antinuclear antibodies, Ro/SSA, La/SSB, and ACE inhibitors, and serum protein electrophoresis was normal. A gallium scan revealed diffuse lymphocytic uptake in the kidneys, salivary gland, lungs, and gastrointestinal tract, thought to be indicative of the diffuse infiltrative lymphocytosis syndrome.[10]

Discussion

This is the first case of the diffuse infiltrative lymphocytosis syndrome reported in a patient not infected with HIV. The patient described here initially presented with salivary gland enlargement due to chronic sialoadenitis. The diffuse lymphocytic infiltration of the salivary glands in this patient meets the recommended histologic criteria for the sicca syndrome.[11] The sicca syndrome is seen in patients with primary Sjögren's syndrome and Sjögren's syndrome due to rheumatoid arthritis, mixed connective tissue disease, systemic lupus erythematosus, and scleroderma. It is also seen in patients with sarcoidosis, chronic graft-versus-host disease, and in those infected with HTLV-I and HIV.[12] Our patient was tested serologically for these diseases with repeated tests for rheumatoid factor, antinuclear antibodies, Ro/SSA, La/SSB, and ACE inhibitors, all of which were negative. Biopsies likewise did not show a malignant neoplasm, vasculitis, granulomata, or acid-fast bacilli, and cultures were negative for tuberculosis. Given this and the lack of clinical findings compatible with any of these diseases, only primary Sjögren's syndrome and diffuse infiltrative lymphocytosis syndrome remain as diagnostic possibilities.

Primary Sjögren's syndrome with extraglandular manifestations is frequently accompanied by nonerosive arthritis, vasculitis, and the presence of autoantibodies, all of which were lacking in our patient. Furthermore, the dramatic and diffuse lymphocytic infiltration of multiple organ systems, including two episodes of biliary tract obstruction, have not to our knowledge been reported in primary Sjögren's syndrome. Finally, the diffuse lymphocytic uptake seen in several organ systems on gallium scanning was thought to be specific for the syndrome in this clinical setting.[10]

In HIV-infected patients, the pathophysiology of diffuse infiltrative lymphocytosis syndrome relates to lymphocytic infiltration of multiple organs with the production of lymphokines such as interferon and other cytokines (interleukin-1, tumor necrosis factor) that cause direct tissue injury.[13] The lymphocytes involved in this syndrome in HIV-infected patients express CD8 and CD29 cell markers. It is thought that lymphocytic infiltra-

tion of the salivary glands in these patients is due either to MHC-restricted recognition of viral proteins expressed in epithelial cells or to retrovirally mediated transactivation of the endogenous gene that is involved in the surface expression of the adhesion molecule ligand.[14-16] Thus, in diffuse infiltrative lymphocytosis syndrome, the lymphocytic proliferative process is an antigenic-driven MHC-determined (involving class I and II loci) host immune response to an element within the HIV virus itself.[17] It is also thought that immunologically intact CD8 lymphocytes with normal interleukin-2 production[18-20] may have a protective immune function by preventing HIV virus replication in HIV-infected patients.[21-23]

Diffuse infiltrative lymphocytosis syndrome is not unique to patients infected with HIV. It has been proposed that infections with other viruses such as herpes simplex virus 6, cytomegalovirus, or other retroviruses could initiate immune responses similar to those described in this patient.[18] Diffuse infiltrative lymphocytosis syndrome should be considered in patients not infected with HIV who present with salivary gland enlargement and extraglandular manifestations. The underlying immune mechanism in such patients should be further investigated.

REFERENCES

1. Itescu S, Brancato LJ, Winchester R: A sicca syndrome in HIV infection: Association with HLA-DR5 and CD8 lymphocytosis. Lancet 1989; 2:466-468

2. Itescu S, Brancato LJ, Buxbaum J, et al: A diffuse infiltrative CD8 lymphocytosis syndrome in human immunodeficiency virus infection: A host immune response associated with HLA-DR5. Ann Intern Med 1990; 112:3-10

3. Adamson TC 3d, Fox RI, Frisman DM, Howell DV: Immunohistologic analysis of lymphoid infiltrates in primary Sjögren's syndrome using monoclonal antibodies. J Immunol 1983; 130:203-208

4. Talal N: The Autoimmune Disease. New York, NY, Academic Press, 1985

5. Mann DL, Moutsopoulos HM: HLA-DR5 alloantigens in different subsets of patients with Sjögren's syndrome and in family members. Ann Rheum Dis 1983; 42:533-536

6. Moutsopoulos HM, Chused TM, Mann DL, et al: Sjögren's syndrome (sicca syndrome): Current issues. Ann Intern Med 1980; 92(pt 1):212-226

7. Manthorpe R, Teppo AM, Bendixen G, Wegelius O: Antibodies to SS-B in chronic inflammatory connective tissue disease—Relationship with HLA-Dw2 and HLA-Dw3 antigens in primary Sjögren's syndrome. Arthritis Rheum 1982; 25:662-667

8. Solal-Celigny P, Couderc LJ, Herman D, et al: Lymphoid interstitial pneumonitis in acquired immunodeficiency syndrome-related complex. Am Rev Respir Dis 1985; 131:956-960

9. Guillon JM, Fouret P, Mayaud C, et al: Extensive T8-positive lymphocytic visceral infiltration in a homosexual man. Am J Med 1987; 82:655-661

10. Rosenberg ZS, Joffe SA, Itescu S: Spectrum of salivary gland disease in HIV-infected patients: Characterization with Ga-67 citrate imaging. Radiology 1992; 184:761-764

11. Greenspan JS, Daniel TE, Talal N, Sylvester RA: The histopathology of Sjögren's syndrome in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol 1974; 37:217-229

12. Vernant JC, Buisson G, Magdeleine J, et al: T-lymphocyte alveolitis, tropical spastic paresis, and Sjögren's syndrome (Letter). Lancet 1988; 1:177

13. Johnson H: Mechanism of interferon gamma production and assessment of immunoregulatory properties. Lymphokines 1985; 11:33-46

14. Green JE, Hinrichs SH, Vogel J, Jay G: Exocrinopathy resembling Sjögren's syndrome in HTLV-1 tax transgenic mice. Nature 1989; 341:72-74

15. Vasmel WL, Zijlstra M, Radaszkiewicz T, Leupers CJ, de Goede RE, Melief CJ: Major histocompatibility complex class II-regulated immunity to murine leukemia virus protects against early T- but not late B-cell lymphomas. J Virol 1988; 62:3156-3166

16. Itescu S, Brancato L, Coregersan PK: Diffuse infiltrative CD8 lymphocytosis in HIV infection is associated with a particular subtype of HLA-DR5 (Abstr). Clin Res 1989; 37:412A

17. Ammann AJ, Cowan MJ, Ball E, et al: Impaired mononuclear cell proliferation in patients with the acquired immunodeficiency syndrome results from the abnormalities of both T-lymphocytes and adherent mononuclear cells. J Clin Immunol 1985; 5:239-241

18. Agah R, Charak BS, Chen V, Mazumder A: Adoptive transfer of anti-cytomegalovirus effect of interleukin-2-activated bone marrow: Potential application in transplantation. Blood 1991; 78:720-727

19. Itescu S: Diffuse infiltrative lymphocytosis syndrome in children and adults infected with HIV-1: A model of rheumatic illness caused by acquired viral infection. Am J Reprod Immunol 1992; 28:247-250

20. Fox RI, Luppi M, Kang HI, Pisa P: Reactivation of Epstein-Barr virus in Sjögren's syndrome. Springer Semin Immunopathol 1991; 13:217-231

21. Walker CM, Moody DJ, Stites DP, Levy AJ: CD8+ lymphocyte can control HIV infection in vitro by suppressing virus replication. Science 1986; 234:1563-1566

22. Tsubota H, Lord CI, Watkins DI, Morimito C, Letvin NL: A cytotoxic T lymphocyte inhibits acquired immunodeficiency syndrome virus replication in peripheral blood lymphocytes. J Exp Med 1989; 169:1421-1434

23. Itescu S, Dalton J, Zhang HZ, Winchester R: Tissue infiltration in a CD8 lymphocytosis syndrome associated with human immunodeficiency virus-1 infection has the phenotypic appearance of an antigenically driven response. J Clin Invest 1993; 91:2216-2225

Topics in Primary Care Medicine

Role of Echocardiography in Primary Care Medicine
Controversies in Hypertension, Atrial Fibrillation, Stroke, and Endocarditis

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Echocardiography has become an important, noninvasive diagnostic tool in the evaluation of patients with cardiovascular disease. Technologic refinements in two-dimensional and Doppler imaging have allowed for precise, noninvasive diagnosis, particularly in patients with valvular, myopathic, and congenital heart disease. The widespread application of echocardiography, including transesophageal imaging, in other areas of cardiac disease is somewhat more controversial. In this review, we discuss the rationale for routinely doing echocardiography in patients with hypertension, atrial fibrillation, stroke, and endocarditis.

Hypertension and Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is recognized as a consequence of hypertension and is predictive of cardiovascular morbidity and mortality. Left ventricular (LV) wall thickness and mass can be measured by M-mode and two-dimensional echocardiography and correlate directly with postmortem measurements.[1]

Epidemiologic data regarding hypertension and LVH have been derived largely from the Framingham Heart Study over the past four decades. Echocardiographic criteria for LVH have been determined by defining normal values in healthy, nonobese subjects with no history of hypertension or cardiac disease.[2] In this healthy population, the prevalence of LVH was 16% in men and 18% in women. This was much higher than its prevalence by electrocardiographic criteria (only 3%).

Among nearly 5,000 patients in the Framingham Heart Study, the prevalence of LVH increased with age; it was detected in 33% of men and 49% of women older than 70 years.[3] Increased LV mass was also associated with increased systolic blood pressure and the incidence of obesity. The presence of valve disease or previous myocardial infarction also predicted the presence of LVH.

Patients with LVH are at increased risk for cardiovascular morbidity and mortality. In a 36-year follow-up, the Framingham study demonstrated that patients with LVH had a fourfold increase in all-cause mortality compared with age-matched controls without LVH.[4] This risk was even higher in patients younger than 65 at the time of enrollment.

A subset of patients from Framingham were evaluated for cerebrovascular events (stroke or transient ischemic attack [TIA]). Left ventricular mass was measured in a group of 1,230 patients with a mean age of 69 who were then observed for eight years.[5] The incidence of stroke or TIA was substantially higher in those with increased LV mass than those with normal LV mass in both men (18.4% versus 5.2%) and women (12.2% versus 2.9%). This increased risk held true after controlling for such variables as age, sex, blood pressure, diabetes mellitus, smoking, cholesterol, or treatment of hypertension.

The relationship between LVH and vascular events persists when all vascular events are evaluated. The Framingham investigators observed more than 3,000 patients older than 40 who were free of cardiovascular disease.[6] Cardiovascular events, defined as angina, myocardial infarction, sudden death, stroke, TIA, or claudication, were more common during the four years of follow-up in patients with LVH. In a similar study, 140 patients with hypertension were observed for five years.[7] In patients with increased LV mass by echocardiography, there was a significantly higher incidence of death, myocardial infarction, stroke, and bypass grafting. Electrocardiographically diagnosed LVH was uncommon and not predictive of these clinical events.

The mechanism by which LVH leads to an increase in cardiovascular events is not certain. Increased LV mass can increase myocardial oxygen consumption and decrease coronary artery flow reserve, predisposing the heart to ischemia. This can lead to fibrosis, systolic or diastolic dysfunction, or arrhythmias. Alternatively, LVH may simply be a marker for hypertension or vascular disease. The association between LVH and stroke, heart failure, and sudden death has led some to think that LVH should be regarded as a grave prognostic sign and not just a compensatory mechanism.[8]

(Amidon TM, Chou TM, Kee LL, Foster E: Role of echocardiography in primary care medicine—Controversies in hypertension, atrial fibrillation, stroke, and endocarditis. West J Med 1996; 164:269-275)

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
LV = left ventricular
LVH = left ventricular hypertrophy
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TTE = transthoracic echocardiography

It is not known if the regression of LVH improves prognosis. There has been a decline in the prevalence of LVH seen on electrocardiography in the past 40 years.[8] This has paralleled a decline in the prevalence of untreated hypertension and an overall decline in cardiovascular mortality. Many small clinical trials have attempted to assess the effect of treating hypertension on the regression of LVH. In one study, a meta-analysis of 109 such studies involving more than 2,000 patients with hypertension was performed.[9] Overall, these patients had a decrease in mean arterial pressure of 15% and a decrease in LV mass of 12%. The drugs used to treat these patients included diuretics, β-blockers, calcium channel blockers, and angiotensin-converting-enzyme (ACE) inhibitors. The greatest degree of LVH regression appeared to occur with the use of ACE inhibitors.

It has been pointed out that many of these LVH regression trials are problematic.[10] The patient group studied is often poorly characterized and small in number. The duration of follow-up is short, and there is often no comparison of drug use with that of placebo. In addition, the echocardiographic images are often not read blindly.

Most echocardiographic trials assessing LVH have used M-mode measurements. This may not be the most accurate method for measuring LV mass. Two-dimensional algorithms have been developed[11] but not widely applied to regression trials. In addition, the variability of LV mass measurements (particularly M-mode) within a person may actually exceed the degree of regression reported[12] and may limit its use in individual patients.

Two large trials have compared various single-drug regimens for the treatment of hypertension and have examined the effects of therapy on the regression of LVH.[13,14] In the Treatment of Mild Hypertension Study, 844 patients were assigned to hygienic therapy and one of five antihypertensive drugs or placebo. Hygienic therapy included weight reduction, restricted sodium and alcohol intake, and exercise. The drug treatments included β-blocker, calcium channel blocker, ACE inhibitor, α-adrenergic blocker, or diuretic. M-mode echocardiography was done at baseline and after four years. All of the drug regimens were effective in lowering blood pressures, and the effect was in addition to the benefits of hygienic therapy. All of the groups showed a 10% to 15% reduction in LV mass, and hygienic therapy alone was as effective in causing the regression of LVH as hygienic plus drug therapy.[15] An exception may have been an additional lowering of LV mass with diuretic therapy.

A second large trial of multiple drug regimens in the treatment of hypertension evaluated the effect of treatment on the regression of LVH.[16] Patients receiving placebo had a slight increase in LV mass after one year, whereas patients receiving active treatment revealed no change in LV mass. Again, an exception was that the group receiving a diuretic had a reduction in LV mass. Whether the measured reduction in LV mass truly represents a regression of LVH or instead is an artifact of the technique used to measure LV mass (with a decrease in LV cavity size due to diuresis) is uncertain.

TABLE 1.—*Routine Echocardiography in Patients With Hypertension for Detection of Left Ventricular Hypertrophy (LVH)*

Arguments For	*Arguments Against*
Presence of LVH portends worse prognosis	Variability of measurement may exceed degree of change expected from regression
Echocardiography is more sensitive for detection of LVH than electrocardiography	Cost
Predicts coronary disease, arrhythmias, and cerebral ischemic events	
May influence therapy for hypertension	

Left ventricular hypertrophy resulting from hypertension confers a worse prognosis. Echocardiography is more sensitive in detecting LVH than a standard electrocardiogram. The effect, however, of the presence of LVH on an individual patient's care is unknown. Although some recommend echocardiography as a simple, noninvasive test to detect end-organ damage, others think that it will not affect the decision to treat hypertension or the aggressiveness of therapy. The arguments for and against the routine use of echocardiography in patients with hypertension are summarized in Table 1.

Atrial Fibrillation

Echocardiography is an important aspect of the initial evaluation of patients with atrial fibrillation. Cardiac chamber hypertrophy or dilation, valve dysfunction, or pericardial disease may be detected. In patients with established atrial fibrillation, echocardiography has been routinely used to assess for the risk of stroke. Atrial fibrillation leads to an increased risk of stroke in nearly 1.5 million Americans. Patients with atrial fibrillation have a rate of stroke of 5% per year, which is six times higher than in patients without the disorder.[17] Atrial fibrillation increases in prevalence and risk with increasing age, and more than half of strokes associated with this dysrhythmia occur in patients older than 75.

Patients with atrial fibrillation can generally be categorized into high and low risk for stroke. Variables that place patients at high risk include hypertension, previous stroke or TIA, diabetes mellitus, heart failure or ventricular dysfunction, increased left atrial size, and advanced age.[18,19]

Most strokes associated with atrial fibrillation are thought to be embolic on the basis of stasis-related thrombus arising in the left atrium, particularly in the

left atrial appendage. Although transthoracic echocardiography (TTE) is insensitive for detecting the presence of left atrial thrombus, transesophageal echocardiography (TEE) is highly accurate. In addition, TEE using a high-frequency transducer can detect spontaneous echocardiographic contrast in the left atrium. This phenomenon is related to erythrocyte aggregation in the presence of stasis and appears as a swirling or smokelike image in the normally clear blood pool. Spontaneous contrast may be seen in such conditions as atrial fibrillation, mitral stenosis, and left atrial enlargement[20] and is strongly associated with thrombus.

Spontaneous echo contrast is common in patients with atrial fibrillation and confers an increased risk of stroke. In one study, 272 patients with nonvalvular atrial fibrillation underwent TEE. Spontaneous echo contrast was detected in 59%.[21] After 18 months of follow-up, patients with spontaneous echo contrast had a substantially higher rate of stroke or embolic event (12% per year) than patients without (3% per year), and survival was decreased. Treatment with warfarin sodium in these patients was associated with a reduction in the incidence of subsequent stroke.

The correlation of spontaneous contrast with embolic events is probably related to an increased aggregation of erythrocytes. The presence of spontaneous contrast has been associated with increased hematocrit and fibrinogen levels.[22] In addition, the degree of spontaneous contrast has been shown to correlate with sedimentation rate, blood viscosity, and the presence of antiphospholipid antibodies.[23]

Transesophageal echocardiography has also been used to measure function of the left atrial appendage. Two-dimensional and Doppler images can detect visible contractions in the appendage. In patients with nonvalvular atrial fibrillation and evidence of reduced left atrial appendage contraction, there is a much higher likelihood of spontaneous contrast or thrombus.[24]

Thus, patients with atrial fibrillation are at risk for stroke, and echocardiography helps identify patients at greatest risk, including those undergoing cardioversion. It has been recognized for decades that patients undergoing cardioversion are susceptible to cardioembolic events. Because of this risk, it is recommended that patients undergoing elective cardioversion of atrial fibrillation of greater than two days' duration be given anticoagulation for several weeks before and after the procedure.[25] A recent review from the Cleveland (Ohio) Clinic evaluated 454 elective cardioversions and detected an incidence of embolic complications of 1.3%.[26] The patients with embolic events had not been anticoagulated, and most of them had been in atrial fibrillation for less than a week.

A recent study addressed the role of left atrial thrombus in cardioversion-related emboli. A total of 94 patients with atrial fibrillation of greater than two days' duration were studied.[27] Left atrial thrombus was identified by TEE in 12 patients. The remaining 82 patients with no thrombus underwent cardioversion with no embolic events. Most of these patients were treated with heparin immediately before cardioversion and warfarin for one month after.

A review of recent studies using TEE before cardioversion of atrial fibrillation revealed a prevalence of atrial thrombi of 2.5% to 23% and a low incidence of systemic emboli in patients without atrial thrombus.[28] In addition, left atrial thrombus may be seen with TEE in as many as 14% of patients with atrial fibrillation of less than three days' duration.[29] There are reports that prolonged therapy with warfarin may be associated with the resolution of thrombus.

The rationale for anticoagulation therapy after cardioversion despite a normal TEE is that the return of atrial function is often delayed. As many as 20% of patients can have a delay in the return of atrial function, and as many as 35% can have the appearance of spontaneous contrast after cardioversion.[30] The recovery of atrial function may take as long as a month, particularly in patients who have had a prolonged (longer than 2 weeks) duration of atrial fibrillation.[31] This applies to patients undergoing pharmacologic as well as direct current cardioversion.

The initial enthusiasm for using TEE to exclude the risk for emboli has been somewhat tempered. A multicenter study from hospitals using TEE-guided cardioversion revealed 17 patients who had embolic events after cardioversion despite no left atrial thrombus detected by TEE.[32] This represents 2.4% of the patients who were screened by TEE before cardioversion. Five of the patients had spontaneous echo contrast before cardioversion, and five had spontaneous contrast or thrombus on TEE repeated after cardioversion. None of these patients had been treated with anticoagulation.

Although at this time TEE cannot be considered an established practice in all patients undergoing cardioversion, a strategy for using TEE in patients with atrial fibrillation of longer than two days' duration (Figure 1) has been proposed.[28] Patients with no evidence of thrombus or spontaneous contrast by TEE can undergo cardioversion with a low likelihood of systemic emboli. This may be particularly useful in patients at high risk for extended anticoagulation. Acute anticoagulation with heparin before cardioversion and anticoagulation with warfarin afterwards is advisable, however. This issue is currently being addressed in the ongoing multicenter Assessment of Cardioversion Using TEE trial, and answers regarding efficacy and cost should be forthcoming. Some arguments for and against the routine use of echocardiography in patients with atrial fibrillation are summarized in Table 2.

Unexplained Stroke and Transient Ischemic Attack

Stroke is a common and often devastating event. There are nearly 500,000 strokes annually in the United States and an equal number of TIAs. It is estimated that nearly 60% of these are due to cerebrovascular disease.[33] The remainder are thought to be due to emboli or remain of uncertain cause.

Stroke and TIA can result from emboli arising from the ascending and transverse aorta or cardiac chambers. In addition, emboli may arise from systemic veins and traverse an intracardiac communication. Echocardiography has been used extensively in the detection of sources of cerebral emboli. In rare cases, an intracardiac tumor such as an atrial myxoma is identified. A variety of more common possible sources of cerebral emboli have been identified and are discussed here.

Left Atrial Thrombus

As mentioned, thrombus in the left atrium can serve as a source of cerebral emboli. The detection of left atrial thrombus requires careful inspection of the left atrial appendage. The incidence of atrial thrombus ranges from 5% to 17% and is most common in patients with mitral stenosis or atrial fibrillation. It has been argued that substantial mitral regurgitation may protect against the formation of thrombus.[34]

Spontaneous echo contrast occurs commonly in patients with mitral stenosis and atrial fibrillation. Similarly, spontaneous contrast has been found in 16% to 18% of patients with unexplained cerebral ischemia.[35,36] Whether the presence of spontaneous contrast necessarily explains the cause of unexplained stroke or TIA remains controversial.

Patent Foramen Ovale

Although the foramen ovale usually closes at birth, autopsy studies suggest that it may remain patent in as much as 25% of the population. A patent foramen ovale may then serve as a source of paradoxic emboli from thrombus that arises in the venous circulation.

Transesophageal echocardiography may be a more sensitive technique than transthoracic imaging for detecting a patent foramen ovale. In addition, the use of agitated saline bubbles or the Valsalva maneuver may enhance its detection. In one study, TTE detected the presence of a patent foramen ovale in only 49% of patients in whom this was apparent by TEE.[37]

The presence of a patent foramen ovale may be of particular interest in young patients with stroke. In one study involving 137 patients with mean age of 37 who had suffered a stroke, patients with alternative explanations—that is, cerebrovascular disease—for stroke, had a prevalence of patent foramen ovale by TEE of 33%. In contrast, in patients with unexplained stroke, the prevalence of patent foramen ovale was 66%.[38] An interesting finding is that the prevalence of this malformation in subjects without cerebral ischemia was 43%.

TABLE 2.—*Routine Echocardiography in Patients With Atrial Fibrillation (AF)*

Arguments For	*Arguments Against*
May detect structural abnormality responsible for cause of AF	Negative study for thrombus does not eliminate risk ofcardioembolic events
Identifies patients at risk for cardioembolic event	Cost
May expedite cardioversion	

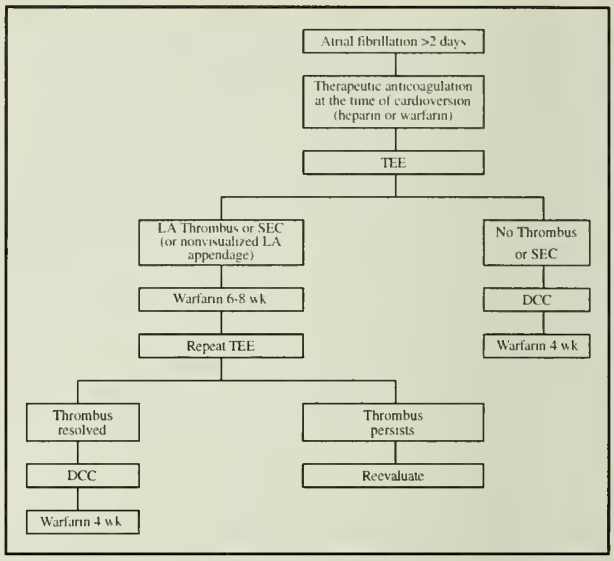

Figure 1.—The graph shows the proposed strategy for transesophageal echocardiographically (**TEE**) guided anticoagulation for patients with atrial fibrillation undergoing elective electrical cardioversion (modified and reprinted with permission from Grimm et al[28]). DCC = direct current cardioversion, LA = left atrium, SEC = spontaneous echocardiographic contrast

In elderly patients with cerebral ischemia, the importance of patent foramen ovale is less certain. In one study, 220 consecutive patients (mean age, 66 years) presenting with cerebral ischemia underwent contrast TEE.[39] In patients older than 50, there was no difference in the prevalence of patent foramen ovale between patients with unexplained stroke and age-matched controls.

Atrial Septal Aneurysm

Atrial septal aneurysm refers to a redundant, hypermobile area of the interatrial septum that usually occurs in the region of the fossa ovalis. The role of atrial septal aneurysm in cerebral embolism is controversial. In a study of 100 patients with unexplained stroke, contrast TEE was used to assess for atrial septal aneurysm and a patent foramen ovale and the findings compared with those in a group of 50 control subjects.[40] Both patent foramen ovale and atrial septal aneurysm were significantly associated with the diagnosis of unexplained stroke, and the odds of stroke was 33 times higher in patients with both disorders than in patients with neither. It has been estimated that atrial septal aneurysm occurs in 2% to 4% of normal controls compared with 11% to 15% of patients with cerebral ischemia.[33] It has also been noted, however, that nearly 80% of patients with atrial septal aneurysm and cerebral ischemia also have other possible echocardiographic sources of emboli (including a prosthetic mitral valve, atrial fibrillation, and a dilated left ventricle).

Mitral Valve Prolapse

The risk of stroke in patients with mitral valve prolapse is controversial. Mitral valve prolapse can be detect-

ed by TTE, and the criteria for diagnosis have become increasingly stringent. Although a review of these criteria is beyond the scope of this article, classic mitral valve prolapse is defined as systolic displacement of one or both leaflets of the mitral valve into the left atrium and thickening and redundancy of the leaflets. Nonclassic mitral valve prolapse lacks leaflet thickening and redundancy. In comparing these two forms, there appears to be no difference in the frequency of stroke,[41] although they differ considerably in the risk of other complications.

The presence of either form of mitral valve prolapse has been suggested as a possible cause of unexplained stroke. A recent study examined 249 young patients (<45 years old) with unexplained stroke and compared them with age-matched controls.[42] The prevalence of mitral valve prolapse was no different in patients with stroke or TIA (3.6%) than in controls (4.7%).

Aortic Atheroma

Aortic atheroma is well recognized as a possible source of peripheral emboli, particularly after catheterization. Spontaneous atheromatous emboli may also be a source of stroke or TIA. In one study, aortic atheroma were detected by TEE in 44% of patients presenting with TIA.[43] More recently, a group of 250 patients with stroke were evaluated with TEE and compared with age-matched controls.[44] Atheromatous plaque was more common in stroke patients (14.4%) than in controls (2%). The odds ratio for stroke among patients with detectable aortic plaque was 9.1. In addition, patients with unexplained stroke had a higher incidence of aortic plaque (28%) than patients with another likely cause of stroke (8%).

Thus, although echocardiography is useful in detecting possible sources of unexplained stroke, TTE is fairly insensitive. In one study, probable or possible sources of emboli were detected less commonly in patients with cerebral ischemia than in comparable controls. In addition, the use of TTE altered clinical management in only 2% of patients.[45] In detecting all possible sources of cerebral ischemia, TEE is more sensitive than TTE[46] and may identify a possible source in as many as 50% to 68% of patients.[35,47] The effect of TEE findings on management decisions, however, has not been studied. Transesophageal echocardiography may also identify patients at increased risk for subsequent cerebral ischemic events.[48] Arguments for and against the routine use of echocardiography in patients with unexplained stroke are summarized in Table 3.

TABLE 3.—*Routine Echocardiography in Patients With Unexplained Stroke*

Arguments For	*Arguments Against*
May identify probable source of cerebral ischemia in <60% of patients with unexplained stroke	TTE much less sensitive than TEE for detecting source of emboli
May identify treatable source of emboli and alter management	Cost

TEE = transesophageal echocardiography, TTE = transthoracic echocardiography

Endocarditis

Echocardiography has been an important component in the evaluation of possible cases of infectious endocarditis. Numerous studies have evaluated the utility of both TTE and TEE. When using surgical or autopsy confirmation as the standard, TTE has a sensitivity for detecting vegetations of 40% to 60% compared with 90% or better with TEE.[49,50] Both modalities have a specificity of greater than 90%. In rare cases, vegetations can be mimicked by such things as myxomatous degeneration of valve leaflets, papillary fibromas, or previous vegetations. The low sensitivity of TTE is particularly evident in those patients with small vegetations (<10 mm) or prosthetic valve involvement.

Transesophageal echocardiography is well suited to detecting complications of endocarditis. This includes leaflet aneurysm or perforation, chordal rupture, abscess, fistula, progressive valve destruction, or prosthetic valve dehiscence. Transesophageal echocardiography was able to detect autopsy-confirmed abscess in 87% of cases versus only 28% by TTE.[51] It may also be particularly well suited to detecting small vegetations.[52]

Echocardiographic findings may also be important in determining prognosis in patients with endocarditis. In one study of 105 patients with endocarditis, vegetation size as determined by TEE correlated with complications.[50] Vegetations greater than 10 mm had a rate of embolization of 47% versus only 19% with vegetations of less than 10 mm. Vegetation size did not correlate with the development of heart failure or death. The location of vegetation was also important, with mitral valve vegetations being more likely to embolize than aortic valve vegetations. Death may be predicted more accurately by clinical variables such as the presence of a prosthetic valve, systemic embolization, or *Staphylococcus aureus* as the culprit organism.[53] In addition to size, vegetation characteristics such as extent, consistency, and mobility have been shown to predict outcome.[54]

Interestingly, the importance of the echocardiographic appearance of a vegetation during the course of antibiotic therapy is less certain. In a study using TTE, 32 patients underwent reimaging at the end of a course of antibiotics. A vegetation was still present in almost 90%, with no change in size in 59% and denser consistency in 52%.[55] Another study used TEE to observe vegetation size during antibiotic therapy. Patients who had an increase or no change in vegetation size were more likely to have embolization, abscess formation, valve replacement, or death than patients with a decrease in vegetation size.[56] An important finding is that a normal TEE does not always exclude the diagnosis of endocarditis. In one study, five patients with a normal initial TEE had evidence of vegetation on a subsequent TEE.[57] Thus, echocardiography, and particularly TEE, is useful for confirming the diagnosis of endocarditis, detecting

TABLE 4.—*Routine Echocardiography in Patients With Endocarditis*

Arguments For	*Arguments Against*
Allows for diagnosis to be established	TTE often insensitive for detecting vegetations
Identifies complications and may indicate need for surgical intervention	Normal TEE does not exclude diagnosis of endocarditis
Identifies embolic risk	Mortality more accurately predicted by clinical variables
Helpful in determining prognosis	Cost

TEE = transesophageal echocardiography, TTE = transthoracic echocardiography

complications, and predicting prognosis. Arguments for and against the routine use of echocardiography in patients with endocarditis are summarized in Table 4. The role of routinely repeating TEE imaging requires further study.

The routine use of echocardiography has altered the definition of endocarditis. A strict case definition was proposed that used only clinical variables.[58] These included blood cultures positive for infective organisms, fever, new murmur, predisposing heart disease, and vascular sequelae. A new case definition has recently been proposed that incorporates positive blood cultures and echocardiographic findings as the major diagnostic criteria.[59] Patients with pathologically confirmed endocarditis were more accurately classified with the new criteria than with the older classification.[60]

Conclusion

Echocardiography has revolutionized the noninvasive examination of patients with common clinical disorders such as hypertension, atrial fibrillation, stroke, and endocarditis. Detailed cardiac anatomy can be readily demonstrated, particularly with TEE. Echocardiography commonly provides unexpected information that may lead to a new diagnosis or alter the treatment strategy.[61] Few data are available, however, regarding the cost-effectiveness of echocardiography in these conditions. It is not certain whether the information gained from echocardiography will ultimately increase or reduce the cost of caring for patients with cardiovascular disease. Pending the results of trials designed to answer this issue, the arguments for and against the use of echocardiography need to be weighed by individual practitioners.

REFERENCES

1. Devereux RB, Reichek N: Echocardiographic determination of left ventricular mass in man—Anatomic validation of the method. Circulation 1977; 55:613-618

2. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP: Echocardiographic criteria for left ventricular hypertrophy: The Framingham Heart Study. Am J Cardiol 1987; 59:956-960

3. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP: Echocardiographically detected left ventricular hypertrophy: Prevalence and risk factors—The Framingham Heart Study. Ann Intern Med 1988; 108:7-13

4. Kannel WB, Cobb J: Left ventricular hypertrophy and mortality—Results from the Framingham Study. Cardiology 1992; 81:291-298

5. Bikkina M, Levy D, Evans JC, et al: Left ventricular mass and risk of stroke in an elderly cohort—The Framingham Heart Study. JAMA 1994; 272:33-36

6. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990; 322:1561-1566

7. Casale PN, Devereux RB, Milner M, et al: Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med 1986; 105:173-178

8. Kannel WB: Left ventricular hypertrophy as a risk factor in arterial hypertension. Eur Heart J 1992; 13(suppl D):82-88

9. Dahlöf B, Pennert K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients—A meta-analysis of 109 treatment studies. Am J Hypertens 1992; 5:95-110

10. Devereux RB, Dahlöf B: Criteria for an informative trial of left ventricular hypertrophy regression. J Hum Hypertens 1994; 8:735-739

11. Byrd BF 3d, Finkbeiner W, Bouchard A, Silverman NH, Schiller NB: Accuracy and reproducibility of clinically acquired two-dimensional echocardiographic mass measurements. Am Heart J 1989; 118:133-137

12. Gottdiener JS, Livengood SV, Meyer PS, Chase GA: Should echocardiography be performed to assess effects of antihypertensive therapy?—Test-retest reliability of echocardiography for measurement of left ventricular mass and function. J Am Coll Cardiol 1995; 25:424-430

13. Neaton JD, Grimm RH Jr, Prineas RJ, et al: Treatment of Mild Hypertension Study: Final results—Treatment of Mild Hypertension Study Research Group. JAMA 1993; 270:713-724

14. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men—A comparison of six antihypertensive agents with placebo: The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med 1993; 328:914-921 [erratum published in N Engl J Med 1994; 330:1689]

15. Liebson PR, Grandits GA, Dianzumba S, et al: Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). Circulation 1995; 91:698-706

16. Gottdiener JS, Reda D, Notargiacomo A, Materson B: Comparison of monotherapy effects on LV mass regression in mild-to-moderate hypertension: Differences between short and long-term therapy (Abstr). J Am Coll Cardiol 1992; 19:85A

17. Hart RG, Halperin JL: Atrial fibrillation and stroke—Revisiting the dilemmas (Editorial). Stroke 1994; 25:1337-1341

18. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk. Ann Intern Med 1992; 116:1-5

19. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. Ann Intern Med 1992; 116:6-12

20. Black IW, Hopkins AP, Lee LC, Walsh WF: Left atrial spontaneous echo contrast: A clinical and echocardiographic analysis. J Am Coll Cardiol 1991; 18:398-404

21. Leung DY, Black IW, Cranney GB, Hopkins AP, Walsh WF: Prognostic implications of left atrial spontaneous echo contrast in nonvalvular atrial fibrillation. J Am Coll Cardiol 1994; 24:755-762

22. Black IW, Chesterman CN, Hopkins AP, Lee LC, Chong BH, Walsh WF: Hematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation. J Am Coll Cardiol 1993; 21:451-457

23. Fatkin D, Herbert E, Feneley MP: Hematologic correlates of spontaneous echo contrast in patients with atrial fibrillation and implications for thromboembolic risk. Am J Cardiol 1994; 73:672-676

24. Mügge A, Kühn H, Nikutta P, Grote J, Lopez JA, Daniel WG: Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: Identification of a subgroup of patients at increased embolic risk. J Am Coll Cardiol 1994; 23:599-607

25. Laupacis A, Albers G, Dunn M, Feinberg W: Antithrombotic therapy in atrial fibrillation. Chest 1992:426S-433S

26. Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG: Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol 1992; 19:851-855

27. Manning WJ, Silverman DI, Gordon SP, Krumholz HM, Douglas PS: Cardioversion from atrial fibrillation without prolonged anticoagulation with use of transesophageal echocardiography to exclude the presence of atrial thrombi. N Engl J Med 1993; 328:750-755

28. Grimm RA, Stewart WJ, Black IW, Thomas JD, Klein AL: Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation? J Am Coll Cardiol 1994; 23:533-541

29. Stoddard MF, Dawkins PR, Prince CR, Ammash NM: Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: A transesophageal echocardiographic study. J Am Coll Cardiol 1995; 25:452-459

30. Grimm RA, Stewart WJ, Maloney JD, et al: Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: Characterization by simultaneous transesophageal echocardiography J Am Coll Cardiol 1993; 22:1359-1366

31. Manning WJ, Silverman DI, Katz SE, et al: Impaired left atrial mechanical function after cardioversion: Relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994; 23:1535-1540

32. Black IW, Fatkin D, Sagar KB, et al: Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation—A multicenter study. Circulation 1994; 89:2509-2513

33. Dressler FA, Labovitz AJ: Systemic arterial emboli and cardiac masses—Assessment with transesophageal echocardiography. Cardiol Clin 1993; 11: 447-460

34. Movsowitz C, Movsowitz HD, Jacobs LE, Meyerowitz CB, Podolsky LA, Kotler MN: Significant mitral regurgitation is protective against left atrial spontaneous echo contrast and thrombus as assessed by transesophageal echocardiography. J Am Soc Echocardiogr 1993; 6:107-114

35. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, Schnittger I: Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke 1991; 22:734-739

36. Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ: Atrial septal aneurysm and stroke: A transesophageal echocardiographic study. J Am Coll Cardiol 1991; 18:1223-1229

37. Di Tullio M, Sacco RL, Venketasubramanian N, Sherman D, Mohr JP, Homma S: Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. Stroke 1993; 24:1020-1024

38. Job FP, Ringelstein EB, Grafen Y, et al: Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. Am J Cardiol 1994; 74:381-384

39. Jones EF, Calafiore P, Donnan GA, Tonkin AM: Evidence that patent foramen ovale is not a risk factor for cerebral ischemia in the elderly. Am J Cardiol 1994; 74:596-599

40. Cabanes L, Mas JL, Cohen A, et al: Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age—A study using transesophageal echocardiography. Stroke 1993; 24: 1865-1873

41. Marks AR, Choong CY, Sanfilippo AJ, Ferre M, Weyman AE: Identification of high-risk and low-risk subgroups of patients with mitral-valve prolapse. N Engl J Med 1989; 320:1031-1036

42. Gilon D, Ferdinando SB, Kistler JP, et al: Mitral valve prolapse: Is it associated with acute ischemic neurologic events? (Abstr) J Am Coll Cardiol 1995; 25:33A

43. Pop G, Sutherland GR, Koudstaal PJ, Sit TW, de Jong G, Roelandt JR: Transesophageal echocardiography in the detection of intracardiac embolic sources in patients with transient ischemic attacks. Stroke 1990; 21:560-565

44. Amarenco P, Cohen A, Tzoudo C, et al: Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994; 331:1474-1479

45. Sansoy V, Abbott RD, Jayaweera AR, Kaul S: Low yield of transthoracic echocardiography for cardiac source of embolism. Am J Cardiol 1995; 75:166-169

46. Albers GW, Comess KA, DeRook FA, et al: Transesophageal echocardiographic findings in stroke subtypes. Stroke 1994; 25:23-28

47. Jones EF, Donnan GA, Calafiore P, Tonkin AM: Transoesophageal echocardiography in the investigation of stroke: Experience in 135 patients with cerebral ischaemic events. Aust NZ J Med 1993; 23:477-483

48. Comess KA, DeRook FA, Beach KW, Lytle NJ, Golby AJ, Albers GW: Transesophageal echocardiography and carotid ultrasound in patients with cerebral ischemia: Prevalence of findings and recurrent stroke risk. J Am Coll Cardiol 1994; 23:1598-1603

49. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB: Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol 1991; 18:391-397

50. Mügge A, Daniel WG, Frank G, Lichtlen PR: Echocardiography in infective endocarditis: Reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol 1989; 14:631-638

51. Daniel WG, Mügge A, Martin RP, et al: Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991; 324:795-800

52. Erbel R, Rohmann S, Drexler M, et al: Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach—A prospective study. Eur Heart J 1988; 9:43-53

53. Jaffe WM, Morgan DE, Pearlman AS, Otto CM: Infective endocarditis, 1983-1988: Echocardiographic findings and factors influencing morbidity and mortality. J Am Coll Cardiol 1990; 15:1227-1233

54. Sanfilippo AJ, Picard MH, Newell JB, et al: Echocardiographic assessment of patients with infectious endocarditis: Prediction of risk for complications. J Am Coll Cardiol 1991; 18:1191-1199

55. Vuille C, Nidorf M, Weyman AE, Picard MH: Natural history of vegetations during successful medical treatment of endocarditis. Am Heart J 1994; 128:1200-1209

56. Rohmann S, Erbel R, Darius H, et al: Prediction of rapid versus prolonged healing of infective endocarditis by monitoring vegetation size. J Am Soc Echocardiogr 1991; 4:465-474

57. Sochowski RA, Chan KL: Implication of negative results on a monoplane transesophageal echocardiographic study in patients with suspected infective endocarditis. J Am Coll Cardiol 1993; 21:216-221

58. Von Reyn C, Levy BS, Arbeit RD, Friedland G, Crumpacker CS: Infective endocarditis: An analysis based on strict case definitions. Ann Intern Med 1981; 94(pt 1):505-518

59. Durack DT, Lukes AS, Bright DK: New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings—Duke Endocarditis Service. Am J Med 1994; 96:200-209

60. Bayer AS, Ward JI, Ginzton LE, Shapiro SM: Evaluation of new clinical criteria for the diagnosis of infective endocarditis. Am J Med 1994; 96:211-219

61. Krumholz HM, Douglas PS, Goldman L, Waksmonski C: Clinical utility of transthoracic two-dimensional and Doppler echocardiography. J Am Coll Cardiol 1994; 24:125-131

Commentary

A Dangerous Profession

JANE A. MORTON, MD, *and* MICHAEL B. JACOBS, MD, *Palo Alto, California*

I (J.A.M.) used to feel fatigued after a hard night on call, but "weary" better describes my mood after last night—a particularly heavy night, even for the winter and a seasoned generalist.

As a member of a large multispecialty clinic, I am told that physicians still hold the reins of control; perhaps this was true in the past, but it is not so clearly the case now. Cynically, I wonder if not too many years ago, the now-wealthy health care reform gurus chuckled to themselves as they predicted the inevitable lemminglike behavior of physicians: "Let them settle into a lifestyle of high mortgages, fine schools for their children, and a sense of control. Then we will take charge, insisting on efficiencies and production quotas so that they will have to scramble to see more patients, extend their hours, and attend our mandatory conferences on working smarter and harder for less and less."

This is how it was last night. Five examining rooms and two of the best nurses, and, yet, each time I emerged from one room, all of the other four were still filled. So around I went—like a rat on a wheel—cutting every corner possible, doing my level best to maintain a courteous demeanor. Later that night, I fulfilled my "gatekeeper" role in an exemplary manner by repeatedly denying authorization for nonurgent emergency department visits. "But it feels like an emergency to me!" implored one desperate mother at 3 in the morning. Is this what I went to medical school for? I thought, unable to relax. It was becoming painfully clear that these gatekeeper responsibilities were inexorably replacing my patient advocacy role. I was trying somehow to be both a supplier and a rationer of care and service; not an easy task, some might say "morally untenable."[1]

I have worked hard before, but something changed for me last night. Was it because of the lingering concerns I had over my patients? Did I miss something? Did I err in my judgment? Or was it because I found myself struggling to hide my impatience, to check myself lest my irritability show in answering perfectly appropriate questions from frightened and concerned patients, to distance myself from the plaintive cries of sick children? Or was it because I was becoming aware of being a pawn in a dangerously out-of-control system and coming perilously close to sacrificing the very core of being a physician, my professionalism and my humanism? The essence of professionalism is altruism, and the essence of humanism is respect, compassion, and sensitivity to our patients.[2] With "bottom-line" care becoming ever more pervasive, I risk compromising both my professionalism and my humanism.

On the Compensation Committee, we talk about ways to encourage our partners to be more productive. But even a race car has brakes, and for good reason. If one goes too fast, someone eventually gets hurt. Who will be the casualties in this new system? Will it be our patients, or will it be physicians as we lose our personal standards and our passion for our profession? Or will it be our families or our friends we increasingly shunt aside because of the ever-expanding demands on our time?

We hear the distant thunder of health care reform, and we choose a defensive position. We increase our malpractice coverage, adopt more stringent surveillance for impaired physicians, and hold mandatory workshops on dealing with "the difficult patient."

The relentless pressure to see more patients in a shorter amount of time and in a more cost-effective way erodes the most precious commodity in our therapeutic armamentarium, the close relationships we establish with our patients. Our "purpose is being replaced by process,"[1] and as a by-product, the quality of our care is being compromised.

The organization of our health care system has profound effects on our ability to care and to heal.[3] Unfortunately, "Today two ethically incompatible cultures exist in medicine. The traditional culture [our calling to care and to heal] is now dominated by a business culture that is eroding the essence of healing relationships."[1(p499)] Until there is some reconciliation between these clashing value systems, each of us will have to draw our own line in the sand, one that recognizes the economic realities of our lives without compromising our integrity, our values, and our commitment to care.

My daughter will soon enter medical school, and she will be introduced to the time-honored dictum of healers: *Primum non nocere*, or "First, do no harm." Although never an easy mandate to follow, in tomorrow's health care system, this will be even more difficult and challenging for her and for all of us striving to uphold the highest ideals of our profession.

REFERENCES

1. Adson MA: An endangered ethic—The capacity for caring. Mayo Clin Proc 1995; 70:495-500

2. Stobo JD, Cohen JJ, Kimball HR, et al: Project Professionalism. Philadelphia, Pa, American Board of Internal Medicine, 1995

3. Scott RA, Aiken LH, Mechanic D, Moravcsik J: Organizational aspects of caring. Milbank Q 1995; 73:77-95

(Morton JA, Jacobs MB: A dangerous profession. West J Med 1996; 164:276)

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Editorials

Prevention of Insulin-Dependent Diabetes Mellitus—Wishful Thinking, or Reality?

In their article elsewhere in this issue of the journal, Charles Verge, MB, BS, PhD, and George Eisenbarth, MD, PhD, review the natural history of insulin-dependent diabetes mellitus (IDDM) before the onset of clinical disease and also comprehensively describe the many treatments being tested worldwide to try to prevent this disease.[1] In this editorial, I will attempt to give additional emphasis to some of the topics that they have introduced.

Their figure that shows the stages in the development of type I diabetes mellitus (Figure 1) appears to depict that over time all persons who reach each respective stage will progress to subsequent stages and eventually to clinical IDDM. In fact, as noted in their text, most people with the genetic susceptibility to IDDM never progress to any of the other stages (including clinical IDDM); each of the autoantibodies associated with IDDM can occur, at least individually, in persons who do not progress to clinical IDDM; and in identical twins of patients with IDDM, immunologic and metabolic markers of IDDM occur in many more than the third who are concordant for clinical IDDM. The major point is that not all nondiabetic persons with the markers of IDDM will progress to clinical disease. The IDDM disease process may begin in some people and then go into remission. Consequently, we may never have the perfect test early in the disease process that can predict eventual clinical IDDM with complete accuracy.

Nevertheless, excellent tools for predicting the risk of clinical IDDM are available. In ICARUS (Islet Cell Antibody Register Users Study), a worldwide collaboration of more than 20 research groups,[2] data have been pooled from 456 islet cell antibody-positive first-degree relatives of IDDM patients. Of these, 108 progressed to clinical IDDM. In these persons, the combination of islet cell antibodies, insulin autoantibodies, age, and first-phase insulin response to glucose allowed a maximum risk of clinical IDDM within five years of nearly 90% to be assigned. Consecutive measurements in individual subjects over time and the addition of HLA determinations, other autoantibodies, and ultimately measures of T-cell function will likely further improve risk prediction. The IDDM disease process is dynamic and complex, probably with spontaneous remissions and relapses. With improved understanding of pathogenesis and an improved ability to accurately assess the status of the IDDM disease process, risk prediction will most assuredly improve as well.

It is easy to imagine an environmental agent or event that initiates or triggers the IDDM autoimmune disease process. But, as Drs Verge and Eisenbarth mention, it is also likely that interaction with the environment may be protective. This point is worth emphasizing. Isolating animals from environmental contact by rearing them under pathogen-free conditions increases the frequency of IDDM in both the nonobese diabetic mouse and the BB rat,[3] strongly suggesting that exposure to one or more environmental agent(s) was protective. The increasing IDDM incidence in some countries and populations cited by Drs Verge and Eisenbarth is possibly due more to the removal of or decrease in environmental protective factors than to an increase in initiating factors. If the major influence of the environment is to initiate, precipitate, or trigger the IDDM disease process, then by definition this must occur early in the disease process. In contrast, if the major influence of the environment is protective, this protection could theoretically occur any time before clinical IDDM. Of course, the two postulated roles for the environment are not mutually exclusive; some environmental factors may be initiators, and others may be protective.

Any attempt to prevent IDDM must have as a guiding principle the importance of balancing the aggressiveness of the treatment against the risk of subsequent IDDM developing. More aggressive intervention is warranted in persons with a high risk, and the obverse is true for persons at lower risk. Theoretically, if an intervention that is low in risk, inexpensive, and convenient could be discovered, perhaps we would treat everyone without even attempting to identify people at increased risk. Vaccines for certain childhood communicable diseases essentially fall into this category.

On the other end of this balance between benefit and risk, broad-spectrum immunosuppressive agents such as cyclosporine, azathioprine, and glucocorticoids have been used in newly diagnosed IDDM patients. Although some improvement in C peptide levels can be observed (as a reflection of the secretion of endogenous insulin), and the frequency and duration of remissions is improved, clinical IDDM recurs even when the drugs are continued long term.[4] Because of this limited success plus the recognized risks and toxicities associated with these drugs, it is unlikely that such broad-spectrum immunosuppressive agents will be able to achieve a positive enough benefit-to-risk ratio for their widespread use.

A precautionary comment for all trials designed to prevent IDDM is also warranted. In nonobese diabetic mice and BB rats, the development of IDDM appears to depend in large measure on the balance between effector and regulatory mechanisms.[3,5] Substrains of the nonobese diabetic mouse and BB rat that do not spontaneously develop diabetes are not missing the diabetogenic effector mechanisms. Rather, these effector mechanisms are kept under control by strong regulatory mechanisms. In both of these animal models, diabetes can be induced or accelerated by immunomodulatory therapy that decreases these regulatory mechanisms.[6,7] Effector cells capable of transferring IDDM to immune-deficient animals have even been isolated from strains of rats without a tendency for spontaneous IDDM.[8] The applicability of these observations in mice and rats to human IDDM is unknown, but, at the least, in designing clinical trials, the possibility that

some forms of immunomodulatory therapy could induce or hasten the onset of clinical IDDM must be considered. To date, the preliminary data available for the two forms of intervention therapy being tested worldwide, parenteral insulin and nicotinamide, show no evidence of possibly increasing the incidence of IDDM.

Finally, I would like to conclude by trying to guess what the results may be of the current ongoing European-Canadian Nicotinamide Diabetes Intervention Trial (ENDIT) and the Diabetes Prevention Trial, Type I (DPT-I). It is likely that both trials will be partially successful; that is, the use of either or both nicotinamide and insulin will prevent IDDM in some, but only some, high-risk persons. But this will represent a most important first step. We will have demonstrated that, at least in some people, IDDM can be prevented. Such a finding will be a tremendous stimulus to understand the mechanism underlying this success, to develop new strategies to improve on this success, and eventually to move these treatments from the research setting into clinical practice. Success in the current and future trials to prevent IDDM will usher in a new era in the treatment of diabetes. Not only will diabetologists treat patients with established diabetes, but they will also use all the combined information from genetic, immunologic, and metabolic tests to determine the risk of a person's subsequent development of IDDM. In persons at increased risk, appropriate therapy will be instituted. Those receiving such preventive therapy will be monitored immunologically and metabolically for the success or failure of their treatment, and if necessary, this treatment will be modified. Success in preventing IDDM may even pave the way for similar attacks and success in preventing other autoimmune diseases.

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REFERENCES

1. Verge CF, Eisenharth GS: Strategies for preventing type I diabetes mellitus. West J Med 1996; 164:249-255

2. McCulloch DK, Bingley PJ, Colman PG, Jackson RA, Gale EAM, the ICARUS Group: Comparison of bolus and infusion protocols for determining acute insulin response to intravenous glucose in normal humans. Diabetes Care 1993; 16:911-915

3. Rabinovich A: Immunoregulatory and cytokine imbalances in the pathogenesis of IDDM: Therapeutic intervention by immunostimulation? Diabetes 1994; 43:613-621

4. Bougnères PF, Landais P, Boisson C, et al: Limited duration of remission of insulin dependency in children with recent overt type I diabetes treated with low-dose cyclosporin. Diabetes 1990; 39:1264-1272

5. Mordes JP, Desemone J, Rossini AA: The BB rat. Diabetes Metab Rev 1987; 3:725-750

6. Charlton B, Bacelj A, Slattery RM, Mandel TE: Cyclophosphamide-induced diabetes in NOD/WEHI mice: Evidence for suppression in spontaneous autoimmune diabetes mellitus. Diabetes 1989; 38:441-447

7. Jiang Z, Handler ES, Rossini AA, Woda BA: Immunopathology of diabetes in the RT6-depleted diabetes-resistant BB/Wor rat. Am J Pathol 1990; 137: 767-777

8. McKeever U, Mordes JP, Greiner DL, et al: Adoptive transfer of autoimmune diabetes and thyroiditis to athymic rats. Proc Natl Acad Sci USA 1990; 87:7618-7622

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*Dr Palmer serves as a consultant to Nichols-Corning Company regarding their islet cell antibody and insulin autoantibody assays, which are used to identify persons at risk for IDDM.

Lessons From the Practice

An 'Out-of-Body' Experience

D. ALLAN MacKENZIE, MD, *Ventura, California*

It was a warm, southern California fall day. This was supposed to be our final "tune-up" bicycle ride in preparation for the World Senior Games. My wife, Mabel, had received a medal in the 1993 cycling events. This was to be *my* year.

Our extra weight had melted off, and our bodies were finally firm. Our time trials in the local competition had gradually improved. We stopped our painful training routines to avoid peaking prematurely for the week of grueling but joyful competition in St George, Utah. The van was packed and fueled; we were physically and psychologically ready to go.

A final 40-mile training loop, we thought, would offset the effects of the 10-hour drive to the competition site. We had completed the toughest part of the hilly ride and were now homeward bound, down the Pacific Coast Bikeway. This north-south bike route straddles the Pacific Coast Highway from the Canadian to the Mexican borders. The scenery, swept clean by the Santa Ana winds, was spectacular. As usual, we saw schools of dolphins traveling in their own channels. We had just shared the last of our food—bananas and PowerBars. I pedaled on alone into the wind and into the final four miles.

In sports, mental imagery is used to imagine yourself performing your sport in perfect form and style. Deep in this reverie, I had just crossed the finish line with a new personal-best time. Suddenly I heard a high-pitched explosion. It sounded like a gunshot, but being on a bicycle, I reasoned that it could have been a spectacular tire blowout. A split second later, I realized that this explosion involved me and that I had become airborne. I reveled in the sudden freedom from gravity. Amazed, I watched my wristwatch being peeled off my wrist, in slow motion, by the brake hood. I could see that the base of my thumb was becoming a fulcrum to the watch strap, so I made a conscious decision to release the bicycle in an effort to save my thumb.

The bicycle was now standing upright and ever so slowly leaving me behind. The right bike shoe, still attached by the clip-in binding, flapped madly on its spindle. Was it spinning clockwise or counterclockwise? I now noted that I was flying through the air on my back, with legs and arms skyward. Bothered by the fact that my horizon was not quite right, I focused on the absence of my shoes and the ragged bike gloves on my wrists.

Desperately I tried to relate all of these facts to the blowout. Then I felt my imaginary spacecraft go into reverse thrust. Massive deceleration forces distorted my face and body. I braced myself, but the impact with terra firma was stunning, sending bolts of lightning from my sacrum into both feet. Mercifully, my mind closed down for a few seconds—and there was no pain. In fact, there was nothingness.

When the cobwebs holding me down cleared, I tried to get up. I needed to understand this "out-of-body" experience. There are no miracles in the 20th century, but maybe this was an exception.

The first person on the scene said, "Get down, man—you just did a back flip." "Why?" I asked. "Because," he explained, "My grandmother drifted into your lane and launched you. You went from being a hood ornament to totally obstructing her windshield. That's why she slammed on the brakes and dumped you. It was totally gnarly."

Suddenly everything made sense again. This was not an extraterrestrial experience. It was, after all, understandable and simple. I lay back down on the road and allowed the white-hot pain to blanket me. The rest is sequel and bad luck. My 81-year-old assailant had just had an eye operation and now had eyedrops and medications on board. The Good Samaritans who happened onto the scene included emergency medical technicians, who peeled my raw body from the harsh gravel road. The ambulance crew and the emergency department team were professional and magnificent. The final tally included remarkable and endless road rash, a fractured thumb, and a fractured sacrum. These injuries were negligible, given the dramatic scenario.

I was admitted to the hospital where I usually work. My wife quietly reminded me that I was not the trauma team leader. When I persisted, she advised the team members to disregard my instructions. I quickly got the idea.

The first 48 hours in the intensive care unit zipped by quickly. The road rash made it impossible to be comfortable. A computed tomographic scan confirmed a displaced, angulated midsacral fracture. Bowel and bladder problems ensued. The sheer joy of being alive seemed to

(MacKenzie DA: An 'out-of-body' experience. West J Med 1996; 164:279-280)

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neutralize the physical pain, and I managed to get myself discharged on day three.

From the moment I arrived home, the sacral pain was constant and unrelenting in intensity. Nights were unbearable. Normally a sound sleeper, I learned firsthand all about insomnia. After a couple of hours of ragged, restless sleep, I was wide awake for the rest of the night.

After four weeks of sleep deprivation, I began to have visual hallucinations—colorful bolts of lightning in broad daylight. This caused me to request relief through the intermittent, epidural administration of medication that my anesthesia colleagues had offered earlier, but that I had rejected. This provided the first true relief from pain sufficient to allow me to get on with my healing and rehabilitation.

What lessons did I learn from this out-of-body experience? First and foremost, fate is fickle. Plans that seem inflexible and important seldom are and can change.

Second, accidents appear to happen in slow motion for the victim, and no two witnesses can agree on the exact sequence of events. The perception is the reality. In this case, the bicycle computer captured the fact that my huge bulk accelerated from 15 to 42 miles per hour before the bicycle tires left the ground.

Third, I was intrigued to learn that mental distraction can be a better analgesic than medication. Sacral fractures are appropriately known as "the painful fracture of necessity." The deep, dull, toothache-like pain is constant and humbling. If all else fails, an indwelling epidural catheter with the use of fentanyl citrate can overcome even sacral fracture pain, at least for three days at a time.

Fourth, we do not know nearly enough about real or imagined pain. You have to have experienced it to appreciate its peculiarity. Your friends, your family, and your job are part of your social safety net. They become an essential part of your analgesia and your healing. Part-time or modified work can be an effective alternative to chemical pain killers.

Fifth, material things like bicycles can be trashed, but healing is the natural propensity of the human body. Help the body by wearing your helmet! You cannot sew or suture the Jell-O-like brain. The only injury-free part of my body was under the shattered shell of my bike helmet.

Finally, we are not only mortal, we are dispensable—all of us.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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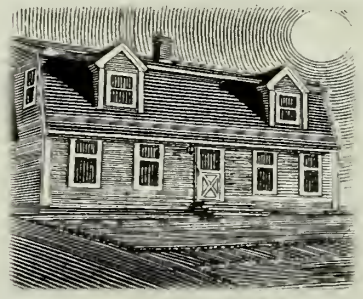

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Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 20-22, 1996, Steam Boat Sheraton, Steam Boat Springs.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1996, Sun Valley Inn, Sun Valley, Idaho.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, New Mexico Medical Society Offices, Albuquerque.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 25-28, 1996. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 26-28, 1996. Tacoma Sheraton, Tacoma.

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* Problem diarrhea defined as severe diarrhea or withdrawals with diarrhea.
† For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect β-lactamase–producing pathogens

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent p

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 1992. *J Chemother* 1993;5(2):67-93. **2.** *Clinical Efficacy Update I-III,* 1995, SmithKline Beecham Pharmaceuticals.

SmithKline Beecham Pharmaceuticals
Philadelphia, PA 19101

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AUGMENTIN® amoxicillin/clavulanate potassium
BRIEF SUMMARY FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.
INDICATIONS AND USAGE: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below
Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin and Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.
Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
ADVERSE REACTIONS: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours. They should receive an additional dose both during and at the end of dialysis.
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.
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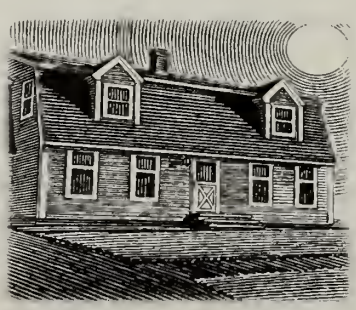

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Sheraton Charleston Hotel, Charleston, SC
May 3-5, 1996

Sixth Annual Current Concepts in Orthopaedics
Omni Inner Harbor Hotel, Baltimore, MD
May 16-18, 1996

20th Annual Lung Symposium
The Cloister, Sea Island, GA
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Ritz-Carlton-Naples, Naples, FL
June 14-16, 1996

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

May 4—**ENT for Primary Care Physicians.** Mayo Clinic-Scottsdale, Ashton B. Taylor Auditorium, Scottsdale. Sat. Contact: Trish Ghan, Mayo Clinic-Scottsdale.

May 4—**Cardiovascular Diagnosis and Treatment: Update 1996.** Arizona Heart Institute at the Phoenician Resort, Scottsdale. Sat. Contact: Cindy Urbaytis, (602) 266-2200, ext 4403.

May 4-5—**Arizona Society of Pathologists Spring Meeting.** University of Arizona College of Medicine at the Hotel Park, Tucson. Sat-Sun. Contact: Patrice Hand, ArMA.

May 6-10—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

May 9-10—**Vascular Access for Hemodialysis V, Ultrasonography Assessment, OST Consideration, Stents, Graphs Lysis.** Ohio State University Medical Center at the Westin La Paloma, Tucson. Thurs-Fri. Contact: (708) 550-0090.

May 18-19—**Arizona Ophthalmological Society Annual Meeting.** Desert Samaritan Medical Center at the Embassy Suites Resort, Scottsdale. Sat-Sun. Contact: Patrice Hand, ArMA.

August 5-10—**1996 Comprehensive Internal Medicine Board Preparation Course.** Marriott's Camelback Inn, Scottsdale. Mon-Sat. Contact: Beverlee Anderson, (602) 267-5366.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 19-24—**UCSD Anesthesiology Review Course.** UCSD at San Diego Princess Resort. Sun- Fri. 37.5 hrs. $600. Contact: Carol Heil, (619) 543-5202.

CARDIOLOGY

June 1—**2nd Annual UCSD Heart Failure Symposium.** UCSD at Sheraton Grande Torrey Pines. Sat. 6.5 hrs. $40. Contact: UCSD, Barry Greenberg, (610) 543-7751.

June 5-8—**Advanced Echocardiography and Doppler Ultrasound 1996.** American College of Cardiology at Hyatt Islandia, San Diego. Wed-Sat. 23.5 hrs. Contact: ACC, Registration Secretary, Extramural Programs Dept, Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

June 28-30—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421- 3756.

DERMATOLOGY

June 7-9—**3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at UCSF. Fri-Sun. Contact: UCSF.

October 12-13—**The Skin From A To Z: Tips on Practical and Office Techniques.** UCSF at UCSF. Sat-Sun. Contact: UCSF.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 2-3—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSD at San Francisco. Sat-Sun. Contact: UCSD.

EMERGENCY MEDICINE

May 13-17—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 17 hrs. $475. Contact: UCSD.

May 14-15—**7th Annual High Risk Emergency Medicine.** American College of Emergency Physicians at Hyatt at Fisherman's Wharf, San Francisco. Tues-Wed. 15 hrs. $299-$499. Contact: Alpen Meeting Service, (800) 451-RISK.

May 31-June 6—**Trauma/Critical Care.** USC at Ritz-Carlton Huntington Hotel, Pasadena. Fri-Sat. 18 hrs. $250. Contact: USC.

June 17-21—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20—**Cost Effective Emergency Medicine.** American College of Emergency Physicians at The Mirage, Las Vegas. Thurs. 8 hrs. $199-$249. Contact: Alpen Meeting Services, (800) 451-RISK.

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency La Jolla, San Diego. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

October 21-25—**Emergency Medicine Symposium I.** UCSD at San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD.

November 11-15—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

June 7-11—**Molecular Steriodogenesis.** UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

EPIDEMIOLOGY/INFECTIOUS DISEASE

May 1-3—**17th Annual Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 17.5 hrs. $410. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

May 15-18—**Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

May 17-21—**Essentials in Primary Care.** Continuing Medical Education Associates at Grand Hyatt on Union Square, San Francisco. Thurs-Sun. 20 hrs. $495. Contact: CMEA, Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

June 7-9—**9th Annual Medical Office Laboratory Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego. Fri-Sun. 23 hrs. $475. Contact: Nancy Geiser, College of Extended Studies, (619) 594-6255.

June 10-12—**2nd Annual Sports and Occupational Medicine in Primary Care: From Prevention to Treatment Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego. Mon-Wed. 20 hrs. $475. Contact: Nancy Geiser, College of Extended Studies, (619) 594-6255.

June 28-30—**San Diego Academy of Family Physicians' 40th Annual Postgraduate Symposium—Family Medicine Update: 1996.** San Diego Academy of Family Physicians at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-$300. Contact: Terry Camarata, (619) 422-1186.

August 2-4—**Managing Respiratory Diseases.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

August 2-4—**Cardiology for the Primary Care Physician.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 5-7—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Doubletree Hotel, Monterey. Fri-Mon. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

October 9-12—**Semiannual Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

INFECTIOUS DISEASE

May 17—**The HIV Challenge: Current Trends & Issues in Management.** UCSD at Olympic Resort Hotel, Carlsbad. Fri. 8 hrs. $75. Contact: Bill Donnelly, (619) 294-3767.

October 26-November 2—**National Infectious Disease Update Conference.** Santa Rosa Kaiser Permanente Medical Center on The Sun Princess Cruise, Western Caribbean. Sat-Fri. 7 hrs. $50-$100. Contact: Infectious Disease Update/SRO, Kaiser Permanente Medical Center, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

INTERNAL MEDICINE

May 9-10—**Practical Aspects of Caring for Alzheimer's Disease Victims.** UCSD at Hilton Beach and Tennis Resort, San Diego. Thurs-Fri. 13 hrs. $326. Contact: UCSD.

September 27-October 2—**Internal Medicine 1996—Fall Program.** Continuing Medical Education Associates at Loews Coronado Bay Resort, San Diego. Fri-Wed. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

NEPHROLOGY

August 2-8—**12th Comprehensive Nephrology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Thurs. 50 hrs. $800. Contact: UCLA.

OPHTHALMOLOGY

May 11—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at Scripps Clinic and Research Foundation, La Jolla. Sat. 7 hrs. Contact: Dept of Academic Affairs, 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OTOLARYNGOLOGY

May 23-25—**Vestibular Adaptation.** UCLA at Miramar Sheraton Hotel, Santa Monica. Thurs-Sat. 17 hrs. $400. Contact: UCLA.

June 22-28—**1995-1996 Skull Base Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles 90057.

June 29-July 4—**Second International Skull Base Congress and the Seventh Annual Meeting of the North American Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Floor, Los Angeles 90057.

July 5-7—**Current Concepts in Allergy and Otolaryngology.** Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital, Continuing Medical Education Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 7-9—**The University of California: Otolaryngology Update 1996.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

PATHOLOGY

May 23-25—**Current Issues in Anatomic Pathology.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

KEY TO ABBREVIATIONS

DREW: Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.

LLU: Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.

STAN: Stanford University, Postgraduate Education, (415) 723-5594.

UCD: University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.

UCI: University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.

UCLA: University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.

UCSD: University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.

UCSF: University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.

USC: University of Southern California, Postgraduate Division, (800) USC-1119.

PEDIATRICS

May 16-18—**29th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 16 hrs. $350. Contact: UCSF.

May 17-19—**1996 Conference on Pediatric Critical Care Transport.** AAP at Doubletree Hotel, San Diego. Fri-Sun. 18 hrs. $380. Contact: CME Registration, AAP, 141 Northwest Point Blvd, PO Box 927, Elk Grove Village, IL 60009-0927.

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians.** UCSD at Hilton Beach and Tennis Resort, San Diego. Thurs-Sat. 15 hrs. $350. Contact: UCSD.

July 19-20—**Fourth Annual Pediatric Update.** Stanford University at Lucile Packard Children's Hospital, Palo Alto. Fri-Sat. 14.5 hrs. $275-$300. Contact: Elinor Meyer, CME Coordinator, Lucile Packard Children's Hospital, 725 Welch Road, Palo Alto 94394. (415) 497-8554.

PLASTIC SURGERY

June 7-9—**The 3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at UCSF. Fri-Sun. Contact: UCSF.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

May 22-24—**3rd Annual Sexual Assault Response Team (SART) Training.** UCD at Red Lion Hotel, Sacramento. Wed-Fri. 19 hrs. $160. Contact: UCD.

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS, (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

November 8-10—**The 42nd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sun. Contact: UCSF.

November 2-3—**Neurology Update.** UCSD at Hotel Del Coronado, Coronado. Sat-Sun. 12 hrs. $350. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

RADIOLOGY

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, Coronado. Sat-Thurs. 22.5 hrs. $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

August 15-18—**Minimally Invasive Therapy of the Brain.** UCSD at Ritz-Carlton Hotel, Marina del Rey. Thurs-Sun. 20 hrs. $495. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 14 hrs. $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 27 hrs. $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

June 26-29—**13th Annual San Diego Shoulder Orthroscopy Meeting.** Tri City Medical Center at Hyatt Regency, La Jolla. Wed-Sat. 24 hrs. $1,375. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD at San Diego. Mon-Sat. 36 hrs. $1,395. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

May 15-17—**New Era of Cardiopulmonary Resuscitation.** USC at Wyndham Hotel, Palm Springs. Wed-Fri. 17 hrs. $345. Contact: USC.

May 31-June 2—**38th Annual Scientific Meeting of the American Association for the Study of Headache.** San Diego. Fri-Sun. Contact: AASH, (619) 845-1720.

June 12 and 14—**ACLS Instructor Course**. American Heart Association at San Leandro. Wed and Fri. 10 hrs. $219.36. Contact: CPR Seminars, (510) 632-6135.

June 25—**12 Lead EKG.** American Heart Association at San Leandro. Tues. 6 hrs. $95. Contact: CPR Seminars, (510) 632-6135.

July 10—**Pre-ACLS Workshop**. American Heart Association at San Leandro. Wed. 6 hrs. $50-$70. Contact: CPR Seminars, (510) 632-6135.

July 19—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs. $100.

July 10 and 21—**ACLS Provider Course.** American Heart Association at San Francisco. 16 hrs. $170. Contact: CPR Seminars, (510) 632-6135.

August 8-11—**38th Annual Postgraduate Refresher Course—Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

August 17-18—**PALS Certification.** American Heart Association at San Leandro. Sat-Sun. 14 hrs. $250. Contact: CPR Seminars, (510) 632-6135.

September 12 & 19—**Arrhythmia Recognition.** American Heart Association at San Leandro. Thurs. 10 hrs. $120.Contact: CPR Seminars, (510) 632-6135.

October 18—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars, (510) 632-6135.

October 19-20—**ACLS Provider.** American Heart Association at San Francisco. Sat-Sun. 16 hrs. $170. Contact: CPR Seminars, (510) 632-6135.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 6-8—**National Stroke Meeting: The Clinical Aspects of Stroke Diagnosis and Treatment.** Medical Education Resources at Red Lion Hotel and Conference Center, Colorado Springs. Thurs-Sat. Contact: Jaclynna Williams, (303) 798-9683. FAX (303) 798-5731.

June 16-22—**42nd Annual Family Practice Review.** University of Colorado Health Sciences Center at Estes Park. Sun-Sat. Contact: U of Colo.

July 26-27—**Adenocarcinoma of the Prostate.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

August 4-9—**21st Annual Primary Musculoskeletal Care Conference.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

September 18-21—**Enhancing Quality and Value in Cardiovascular Care.** University of Colorado Health Sciences Center at Vail. Thurs-Sat. Contact: U of Colo.

October 28-November 1—**42nd Annual Family Practice Review (Repeat of June program).** University of Colorado Health Sciences Center at Denver. Mon-Fri. Contact: U of Colo.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting**. Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 2-5—**1996 Southwest Allergy Forum.** Hilton of Santa Fe, Santa Fe. Thurs-Sun. Contact: UNM SOM.

July 8-11—**39th Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Mon-Thurs. Contact: Ann Woodrow, CAE, NMAFP, 2309 Renard SE, Albuquerque 87106. (505) 243-4560.

July 11-14—**New Choices, New Challenges, Psychopharmacology in the Primary Care Setting.** La Fonda Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**Podiatric Surgical Seminar.** Hotel Santa Fe, Santa Fe. Wed-Thurs. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 26-28—**How to Diagnose and Treat Arrhythmias for the Primary Care Physician.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

August 2-4—**Practical Pediatrics.** La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 15-18—**Primary Care for the Aging Person.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 22-25—**Implementing Change in Patient Behavior and Clinical Practice.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 3-6—**Building "Virtual" Integrated Delivery Systems: Thriving in an Advanced Healthcare Market.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

June 23-24—**Otolaryngology in the Intermountain West**. University Park Hotel, Salt Lake City. Sun-Mon. 5 hrs. $50. Contact: UUSM.

July 13-20—**Update in Clinical Microbiology and Immunology**. Snow King Resort at Jackson Hole, Wyoming. Sat-Sat. 25 hrs. Contact: UUSM.

August 9-10—**Advanced Obstetrical Life Support**. University Park Hotel, Salt Lake City. 24 hrs. $450. Contact: UUSM.

August 12-16—**Northwest Neuroradiology and Advanced MR Imaging Course**. Pan Pacific Hotel, Vancouver, British Columbia. Mon-Fri. 42 hrs. $1,250. Contact: UUSM.

September 20—**Ophthalmology: Clinical Faculty Day**. Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological**. University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

October 7-9—**Preconference Workshop**. Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging**. University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

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CH:	Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.
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ETS:	Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 2—**Pesticide Medicine.** Yakima. Thurs. Contact: NW Center for Occupational Health & Safety, (206) 543-1069.

May 5-8—**Congenital Heart Disease in the Adult**. Stevenson. Sun-Wed. Contact: American College of Cardiology, (800) 257-4739.

May 9—**Hypertension.** Seattle. Thurs. Contact: U/W.

May 16—**Women's Health Care.** Seattle. Thurs. Contact: Providence/Seattle Medical Center, (206) 320-2552.

May 31—**Infectious Diseases Update.** Seattle. Fri. Contact: U/W.

June 3-7—**Sampling & Evaluating Airborne Asbestos Dust.** Seattle. Mon-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

June 7—**Nuts, Bolts, and Innovation in Gastrointestinal Disease III.** Pierce County College of Medical Education, Tacoma. Fri. Contact: PCMS CME.

June 9-12—**Genome Information: Ethical Implications.** Seattle. Sun-Wed. Contact: U/W Medical History, (206) 616-1864.

June 12-14—**4th Annual Pacific Northwest Cardiovascular Symposium.** Seattle. Wed-Fri. Contact: Providence/Seattle Medical Center, (206) 320-2552.

June 20-21—**ACLS.** Pierce County College of Medical Education, Tacoma. Thurs-Fri. Contact: PCMS CME.

June 28—**Alzheimer's Disease.** Seattle. Fri. Contact: U/W.

June 28—**Cross Cultural Medicine: Healing and Communication in Diverse Cultures.** Tacoma. Fri. Contact: Multicare CME. (206) 552-1221.

July 12-13—**Orthopedic Traumatology.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

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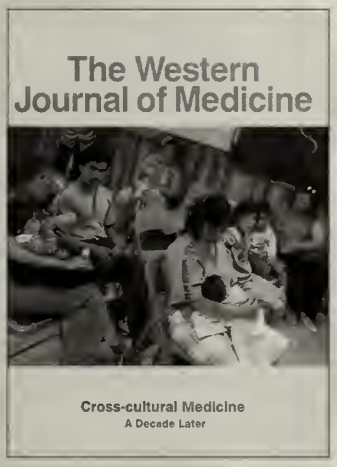

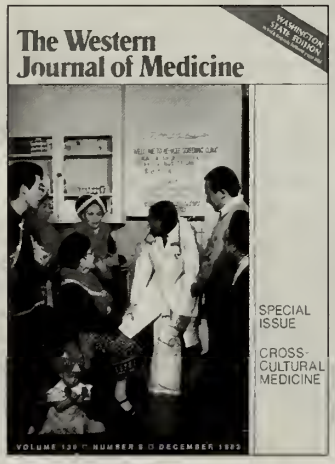

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Articles

Cost-Effective Therapy for Hypertension

WILLIAM BARRIE, MD, *Ann Arbor, Michigan*

The costs of treating hypertension are out of control. The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure and others recommend the use of diuretics and β-blockers as first-line agents. Newer drugs such as calcium channel blockers, α-blockers, and angiotensin-converting-enzyme inhibitors have improved metabolic profiles, but have not been proved in long-term, randomized, controlled trials to reduce morbidity and mortality. Our General Medicine Clinic has gradually shifted toward prescribing the newer agents. We reviewed our drug use, evaluated the literature, and made recommendations in the form of guidelines. Clinicians' concerns included quality-of-life issues, sexual dysfunction, metabolic changes—lipids, potassium, insulin resistance—and others. These concerns were addressed, and a consensus was reached. Our goal is to streamline therapy, reduce costs, and provide proven effective medication.

(Barrie W: Cost-effective therapy for hypertension. West J Med 1996; 164:303-309)

The treatment of hypertension is a daily part of primary care. About 50 million Americans have hypertension. Of these, 30 to 34 million are receiving drug therapy. Total health care costs for hypertension have been estimated at $15 billion per year. Medication cost is an important cause of noncompliance. In recent years, there has been a shift from older, well-studied, and inexpensive drugs to newer and more expensive medications. In the General Medicine Clinic of the Veterans Affairs (VA) Medical Center, Ann Arbor, Michigan, we have reduced the use of diuretics and β-blockers in favor of calcium channel blockers, α_1-blockers, and angiotensin-converting-enzyme (ACE) inhibitors. The new agents have theoretical advantages, but remain unproved in terms of morbidity and mortality.

The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has been providing recommendations to clinicians since 1977. During this time, there has been a steady decline in the mortality rates for stroke (57% reduction) and coronary artery disease (50% reduction).[1] Patients' awareness of hypertension, drug treatment, and adequate control has increased. Lifestyle modifications—weight loss, exercise, and moderation of dietary salt and alcohol intake—are recommended for the prevention and management of high blood pressure.

Treatment guidelines provide a means to streamline therapy, reduce costs, and provide effective medication. After discussions with clinic staff—staff physicians, nurse practitioners, physician assistants, and residents in internal medicine—we developed guidelines for hypertension therapy (Figure 1). The recommendations were evidence based. We discussed clinicians' concerns with the drugs, presented data regarding these concerns, and modified the guidelines so that a consensus was reached. This article demonstrates how local guidelines can be developed from available evidence and national guidelines and tailored to the needs and concerns of a particular community.

Guidelines of the Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure

The most recent JNC report, its fifth, published in 1993, focused on the evaluation, classification, primary prevention, and drug therapy for hypertension.[1] Two major changes from previous JNC reports included a new classification system and a revised treatment algorithm. The old classification of hypertension as mild, moderate, or severe focused on the diastolic blood pressure. The new system is in stages, which incorporate both systolic and diastolic blood pressures. Accumulating data show the systolic blood pressure to be a strong predictor of cardiovascular risk.

Diuretics and β-blockers are now the preferred drugs for first-line therapy. Angiotensin-converting-enzyme inhibitors, calcium channel blockers, α_1-blockers, and α_1-β–blockers are recommended for use as alternative treatments. The JNC's fourth report included ACE inhibitors and calcium channel blockers as first-line drugs.[2] Costs were not considered, although β-blockers and diuretics are much less expensive than the other two classes of drugs. The recommendations were based on available evidence from long-term trials showing reduced morbidity and mortality with these agents. The Canadian and British hypertension societies have made similar recommendations.[3,4]

From the Department of Veterans Affairs Medical Center and the University of Michigan School of Medicine, Ann Arbor.
Reprint requests to William Barrie, MD, Dept of Internal Medicine, Veterans Affairs Medical Center, 2215 Fuller Rd, Ann Arbor, MI 48105.

ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
CHD = coronary heart disease
CI = confidence interval
COPD = chronic obstructive pulmonary disease
HDL = high-density lipoprotein
JNC = Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure
MRC = Medical Research Council
SHEP = Systolic Hypertension in the Elderly Program
VA = Veterans Affairs

In 1990 a meta-analysis of previous hypertension trials showed a 42% reduction in the incidence of stroke (95% confidence interval [CI], 33% to 50%) and a 14% reduction in the incidence of coronary heart disease (CHD) (95% CI, 4% to 22%).[5] The reduction in the incidence of stroke met expectations based on epidemiologic data of lowering diastolic blood pressures 5 to 6 mm of mercury over five years, but the CHD results fell short (expected 20% to 25% reduction). The expected CHD reduction was based on long-term (>10 years) follow-up. The relatively short duration (<5 years) of the trials may explain some of this difference. Recent studies have shown a more impressive reduction in the CHD incidence. When the results of the Systolic Hypertension in the Elderly Program (SHEP),[6] the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension),[7] and Medical Research Council (MRC)[8] trials are added to those of 14 previous trials,[9] the reduction in the incidence of CHD events is 16% (95% CI, 8% to 23%). The better results of recent trials may reflect lower doses of thiazides, the use of potassium-sparing diuretics, and potassium supplementation. A recent meta-analysis of hypertension therapy in elderly patients (aged 60 and older) showed a 12% reduction in overall mortality, a 36% reduction in stroke mortality, and a 25% reduction in CHD mortality.[10]

Drug Use

The outpatient pharmacy budget for our General Medicine Clinic in 1994 was $1.8 million. More than 30% was devoted to cardiovascular drugs. Table 1 gives a list of VA drug acquisition costs versus local pharma-

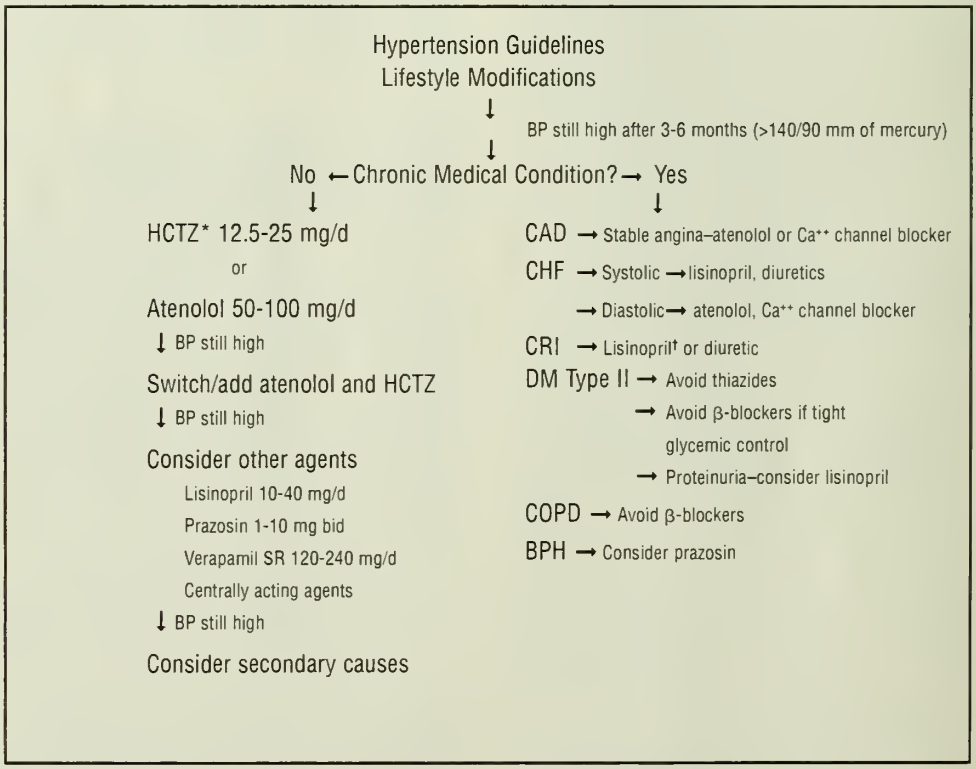

Figure 1.—Guidelines for the treatment of hypertension are outlined. These guidelines were developed for mild to moderate hypertension (essential). Patients with severe hypertension or target organ damage may require more aggressive treatment. Lifestyle modifications include weight loss, regular aerobic exercise, no added salt (2 grams of sodium), diet, and reduced alcohol intake (≤2 beers/day). *Potassium-sparing diuretics may be used as a substitute. †Use caution when starting lisinopril therapy in patients with chronic renal insufficiency (CRI) or coronary artery disease (CAD) because it may precipitate azotemia, hyperkalemia (especially with potassium-sparing diuretics or nonsteroidal anti-inflammatory drugs), or hypotension. Special situations include the use of β-blockers for migraines, or the use of α-blockers for symptomatic benign prostatic hypertrophy (BPH). bid = twice a day; BP = blood pressure; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease—emphysema, chronic bronchitis, asthma; DM = diabetes mellitus; HCTZ = hydrochlorothiazide, tid = 3 times a day

TABLE 1.—*Drug Costs Per Year at the Veterans Affairs Medical Center Versus Red Book 1995**

Agent (Trade Name)	*Veterans Affairs, $*	*Red Book AWP, $*
Hydrochlorothiazide, 25 mg/d	1.06	5.40
Hydrochlorothiazide and triamterene (Dyazide), 50/25 mg/d	21.12	137.64
Atenolol, 100 mg/d	14.08	45.41
Metoprolol tartrate (Lopressor), 100 mg bid	39.42	226.30
Propranolol HCl, long acting, 120 mg/d	199.93	323.76
Prazosin HCl, 2 mg bid	24.64	85.92
Doxazosin mesylate, 8 mg/d	196.42	351.96
Lisinopril, 20 mg/d	91.87	300.96
Captopril, 50 mg bid	44.35	860.64
Verapamil, sustained release, 240 mg/d	83.07	347.28
Diltiazem HCl, 90 mg tid	81.31	281.12
Extended release, 300 mg	495.96	767.92
Nifedipine (Procardia), Extended release, 90 mg/d	400.22	885.36
Amlodipine besylate, 10 mg/d	438.59	718.01
Clonidine HCl, 0.2 mg bid	5.63	16.20

bid = twice a day, HCl = hydrochloride, tid = 3 times a day

*The Veterans Affairs costs (March 1996) represent acquisition costs only. The Red Book (Medical Economics Data, Inc, Montvale, NJ) average wholesale price (AWP) represents recommended pharmacy charge less the drug-dispensing fee. Captopril is now generic, and its 1996 AWP will be substantially lower.

cy charges. Buying in bulk and government contracts reduce prices. As shown in the table, diuretics and β-blockers are much less expensive. Within drug classes, there are often pronounced differences in cost. Atenolol is much less expensive than metoprolol or long-acting propranolol at our institution. There were also differences between the pharmacies in relative costs. Prazosin is much cheaper than doxazosin at the VA, yet more expensive at a local pharmacy.

Cardiovascular drug use and cost are shown for January 1995 (Figures 2 and 3). Calcium channel blockers are our number one class, with most prescriptions being for diltiazem hydrochloride, amlodipine besylate, and extended-release nifedipine GITS [gastrointestinal therapeutic system]. We have had a steady increase in the prescribing of ACE inhibitors and calcium channel blockers. Prescribing patterns across the United States have changed in a similar direction. A study of temporal patterns in antihypertensive drug use among elderly patients found that patients with newly treated hypertension were half as likely to receive β-blockers or diuretics and twice as likely to receive ACE inhibitors or calcium channel blockers as patients with previously treated hypertension.[11] The Cleveland (Ohio) VA Medical Center has encountered nearly identical changes and has responded by developing guidelines.[12] From 1988 to 1992, the percentage of its budget devoted to calcium channel blockers and ACE inhibitors increased from 9.4% and 5.5% to 20.5%, and 8.9%, respectively.

Numerous factors influence clinicians' decisions on medication use, including advertising. At our facility, our most expensive and commonly used antihypertensive agents have also been those most promoted by drug representatives. They interact with staff and frequently provide lunches and books for the clinic. Conceding that there is no such thing as a "free lunch," the physician staff has recently agreed to eliminate drug representatives and drug lunches from the General Medicine Clinic.

Concerns With Guidelines

Concerns about diuretics and β-blockers need to be addressed. Many perceived side effects are not supported by the literature. These issues include quality of life, sexual dysfunction, drug effectiveness, alteration in lipids, insulin resistance, and hypokalemia.

Quality of Life

Many of the staff felt that the use of diuretics and β-blockers reduces patients' quality of life. An excellent review has been done on quality of life and hypertension.[13] Many patients with hypertension have symptoms that include headache, blurred vision, unsteadiness, sexual dysfunction, and cognitive impairment. Antihypertensive therapy generally reduces symptoms and improves patients' quality of life. Quality-of-life measures include well-being, mental health, energy, cognitive or motor function, and sexual function.

The use of methyldopa and propranolol hydrochloride worsen the quality of life. Taking propranolol may increase the risk of depression. In contrast, β_1-selective β-blockers (β_1-blockers) have effects on quality-of-life measures similar to those of calcium channel blockers and ACE inhibitors. A recent study evaluating quality of life and cognitive and motor function for hydrochlorothiazide, enalapril, and propranolol showed no impairment in cognitive or motor skills (although propranolol did reduce overall quality of life).[14] Fatigue is a common complaint before medication. No differences in the incidence of fatigue were noted between the use of β_1-blockers and that of ACE inhibitors.

The Treatment of Mild Hypertension Study compared five drug classes with placebo.[15] Quality-of-life measures improved with drug therapy, but those of only chlorthalidone and acebutolol reached significance ($P < .05$). Erectile dysfunction occurred in 16.5% of those taking placebo versus 13.1% of those on drug therapy ($P = .02$) (10.4% for acebutolol, 17.3% for chlorthalidone). The Trial of Antihypertensive Interventions and Management (TAIM) study evaluated quality of life and sexual dysfunction when taking placebo, chlorthalidone, or atenolol.[16] Both treatment groups had improved quality of life, although the chlorthalidone group had more erection problems (17% versus 7% in placebo, $P = .005$). A recent review on sexual dysfunction with antihypertensive medications concludes that sexual dysfunction at baseline is common in men with hypertension and increases with the use of diuretics.[17] Data regarding the use of propranolol are less convincing. A VA cooperative study compared six drug classes

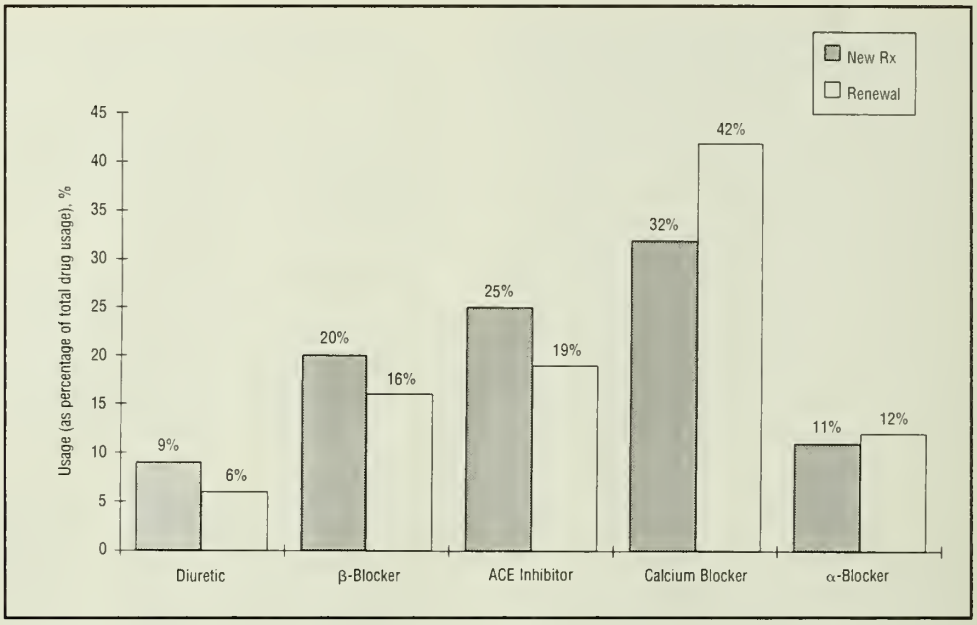

Figure 2.—The graph shows the cardiovascular drug use in general medical outpatients in January 1995. Miscellaneous drugs made up 3% of new and 5% of renewal prescriptions. ACE = angiotensin-converting enzyme

and found no differences in erectile dysfunction.[18] In this study, only clonidine and prazosin therapy were associated with increased overall side effects. Hydrochlorothiazide and atenolol had the lowest dropout rates for side effects.

Effectiveness

The newer antihypertensive drugs are often perceived as more effective. Most studies show similar blood pressure responses using different drug classes.[15,18] An individual drug adequately controls blood pressure in 40% to 60% of patients with mild to moderate hypertension. In the VA cooperative trial, African Americans responded better to the use of diltiazem (although many required the highest dose). Older patients responded well to all drug classes.

Lipids

Of our hypertensive patients, 40% to 50% have hyperlipidemia. Clinicians are often uncomfortable prescribing diuretics and β-blockers to these patients. Thiazides cause a short-term increase in total cholesterol and low-density lipoprotein levels of 5% to 7%. Long-term diuretic-based trials, however, show minimal change from the placebo group.[19] In the Treatment of Mild Hypertension Study, cholesterol levels in the group taking chlorthalidone (15 mg per day) were elevated at one year, but returned to baseline (placebo) over the four-year study.[15] β_1-Blockers may increase triglyceride levels and lower high-density lipoprotein (HDL) levels. In the Treatment of Mild Hypertension Study, the HDL levels in patients taking acebutolol remained unchanged, whereas in other groups they increased 1 to 2 mg per dl. Many staff have favored the use of α-blockers, which raise the HDL:total cholesterol ratio by 10% and decrease triglyceride levels by 10%.[20] Regimens of ACE inhibitors and calcium channel blockers have minimal effect on lipids.

The minor degree of long-term lipid changes with the use of diuretics and β-blockers is of uncertain importance. These changes would not affect management strategies in hyperlipidemia patients in most cases. Until long-term data confirm improved morbidity and mortality with the newer drugs, "soft" data (that is, metabolic variables) should not be used to make decisions on drug selection.

Insulin Resistance and Diabetes Mellitus

Diabetes mellitus is prevalent in this population. About 15% of elderly patients with hypertension have diabetes. The use of thiazides increases insulin resistance, particularly when used in high doses or causing hypokalemia. β_1-Blockers have minimal effect on insulin resistance, but can reduce the adrenergic symptoms of hypoglycemia. Calcium channel blockers are neutral. α-Blockers and, to a lesser extent, ACE inhibitors decrease insulin resistance. In most of our diabetic patients, their diabetes is controlled with diet, oral medication, or once- or twice-a-day insulin regimens. Tight control with insulin pumps or frequent injections is uncommon. In patients without frequent hypoglycemia, we have used β_1-blockers without problems.

Diuretic use is more controversial. In a cohort study, cardiovascular mortality was higher in patients with hypertension and diabetes mellitus treated with diuretics than those treated with other agents or no medication.[21]

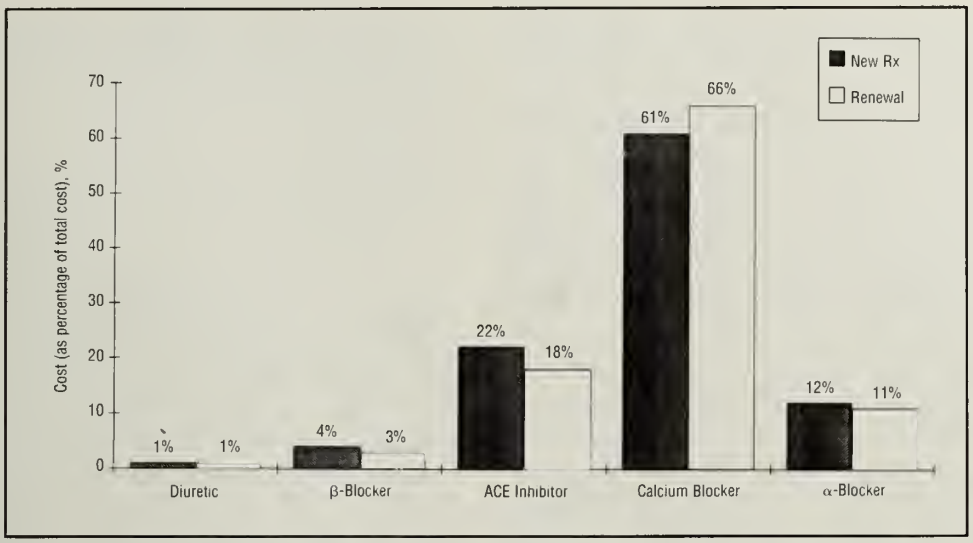

Figure 3.—The graph shows the relative cost of cardiovascular drugs in general medical outpatients in January 1995. Miscellaneous drugs made up 1% of new and of renewal prescription costs. ACE = angiotensin-converting enzyme

The type of diuretic, dose, and metabolic consequences were not given. The study's conclusions are also weakened by the lack of baseline data on target organ disease in each group. The JNC's Fifth Report and the British Hypertension Society recommend using diuretics with caution, and the Canadian Hypertension Society considers thiazides as second-line antihypertensive agents.[1,4,22] A case-control study found that thiazides did not increase the risk of diabetes therapy beyond that of other blood pressure agents.[23] Large diuretic-based trials, including SHEP and the Hypertension Detection and Follow-up Program,[24,25] have shown that the diabetic subgroup benefits from therapy similar for that for patients without diabetes.

Diabetic patients are at an increased risk for renal disease. Administering ACE inhibitors and some calcium channel blockers (non-dihydropyridine) slows the progression of diabetic renal disease (glomerular filtration rate decline and albuminuria).[26] Many staff thought we should give all diabetic patients ACE inhibitors to reduce the risk of renal disease. Their use in diabetic patients with normal urinary albumin concentrations to delay renal disease, however, remains unproved. One study compared the use of captopril with conventional therapy in hypertensive patients with diabetes type II.[27] Blood pressure responses were similar. In patients with microalbuminuria, urinary albumin excretion improved with captopril use more than with conventional therapy. In diabetic patients with normal albumin concentrations, there was no difference. Renal function remained the same in both treatment groups over the 36-month study.

Hypokalemia

Hypokalemia is a major concern with thiazides. A dose-response curve between nonpotassium-sparing diuretics and serum potassium levels exists.[28] Data on serum magnesium and intracellular magnesium-potassium levels are sparse. A case-control study concluded that high-dose thiazide therapy is associated with an increased risk of sudden cardiac death.[29] The combined use of low-dose thiazide and potassium-sparing agents was associated with the lowest risk. This may explain the better CHD results in recent trials,[6-8] which used lower doses of diuretics. The MRC trial participants receiving low-dose thiazide with a potassium-sparing agent had a 40% reduction in CHD mortality.[8] High-dose thiazides may partially explain the inability of older hypertension trials to achieve the expected reduction in CHD mortality.

Our staff is in general agreement on the use of high-dose thiazides. If patients do not respond to a regimen of low-dose hydrochlorothiazide (12.5 to 25 mg) plus or minus potassium-sparing agents, then other drugs are tried or added.

Left Ventricular Hypertrophy

Left ventricular hypertrophy is common in hypertensive patients (30% by echocardiogram) and increases with severity and age. Many clinicians thought that certain drug classes were superior in this group, including β-blockers, calcium channel blockers, and ACE inhibitors. A recent review of hypertension and the heart found that all antihypertensive agents are effective in reducing left ventricular hypertrophy (exceptions include minoxidol and hydralazine).[30] Some drug classes reduce left ventricular mass more rapidly. In the Treatment of Mild Hypertension Study, all drug classes reduced left ventricular hypertrophy, with the largest reduction in the group on chlorthalidone therapy.[15]

β-Blockers Versus Diuretics

Of the preferred drugs—β-blockers or diuretics—is one better? We might expect β-blockers to be more effective in reducing CHD mortality. They reduce

mortality (about 20%) when used after myocardial infarction. Three large trials comparing predominantly diuretic-based with predominantly β-blocker–based therapy showed no major differences in the rates of stroke, CHD, or vascular death.[5] The Metoprolol in Patients with Hypertension Study showed reduced total and cardiovascular mortality in men using metoprolol compared with moderately high-dose thiazides.[31] This study was unblinded. The MRC trial in older adults showed more benefit from the use of low-dose thiazide plus potassium-sparing diuretics than with atenolol.[8] This issue remains unsettled.

Specific Indications for Alternative Drug Classes

There are many situations where administering diuretics and β-blockers is not preferred. The use of thiazides is contraindicated in patients with gout. Treatment with β-blockers is relatively contraindicated in patients with congestive heart failure, asthma, and symptomatic chronic obstructive pulmonary disease (COPD). Patients with evidence of mild COPD may tolerate taking β_1-blockers. Symptoms of benign prostatic hypertrophy may respond to the use of α-blockers. Angiotensin-converting-enzyme inhibitors are first-line agents for the treatment of congestive heart failure. Morbidity and mortality in patients with coronary artery disease and myocardial infarction have improved with the use of β-blockers, calcium channel blockers, and ACE inhibitors. The use of ACE inhibitors may slow the progression of chronic renal insufficiency more than other antihypertensive agents.[32]

Cost Containment

Cost containment is a growing concern. The cost per year of life saved from treating mild to moderate hypertension has been estimated at $40,000 for younger adults and less in older adults. These costs compare well with other preventive strategies. A computer simulation on costs for treating patients (aged 35 to 64, with diastolic blood pressures >95 mm of mercury and no known coronary artery disease) calculated the costs per year of life saved with various monotherapies.[33] The results were $10,900 for propranolol, $16,400 for hydrochlorothiazide, $31,600 for nifedipine, $61,900 for prazosin, and $72,100 for captopril. Studies of this type, however, must make numerous assumptions using models and methods of cost-effective analysis that may be based on insufficient data.

A retrospective study of drug costs looked at total costs of treating hypertension with various regimens.[34] These costs included those for acquisition, supplemental drugs, laboratory tests, clinic visits, and complications. The costs per year of treatment were $895 for β-blockers, $1,043 for diuretics, $1,165 for α_2-agonists, $1,243 for ACE inhibitors, $1,288 for α-blockers, and $1,425 for calcium channel blockers.

Summary

The purpose of this review was to evaluate our antihypertensive drug use and to develop guidelines to provide optimal therapy based on available evidence. Drug acquisition costs were included, but were only one component in the recommendations. By using a team approach and including the staff in the development of the guidelines, we have addressed individual concerns and increased chances of guideline compliance. The guidelines are voluntary. Periodic drug use studies will be done to assess the effects of the guidelines.

The guidelines (Figure 1) emphasize lifestyle changes, with a goal blood pressure of 140/90 mm of mercury.[1,35,36] Hydrochlorothiazide (12.5 to 25 mg) and atenolol (25 to 100 mg) are first-line drugs. Chlorthalidone and potassium-sparing thiazide diuretics are considered reasonable alternatives. The clinic staff were most familiar with hydrochlorothiazide in the non–potassium-sparing diuretic agents. Atenolol was chosen over metoprolol because of cost differences at our facility. Second-line drugs were recommended based on the costs within their category. Specific indications for alternative antihypertensive agents in coexisting medical problems were addressed.

After five months of guideline use, several changes have been noted. The number of calcium channel blocker prescriptions has decreased 34%. The use of ACE inhibitors has not changed. The number of prescriptions for thiazides, β-blockers, and α-blockers increased 37%, 51%, and 43%, respectively. Our total number of prescriptions for these agents has increased, without a substantial change in our population base. We attribute this change to more aggressive blood pressure treatment. Our current drug costs are 18% lower than six months before. We anticipate more change as staff members become more comfortable with the guidelines. The clinic staff has generally had positive responses to the guidelines. One problem area has been taking patients off their regimens of ACE inhibitors or calcium channel blockers, which have previously been first-line drugs or monotherapy. Many of these patients feel well and have good blood pressure control. Clinicians feel uncomfortable switching them to guideline-based therapy (diuretic or β-blocker). My experience has been that most patients are open to change when the guidelines are explained.

We are fortunate to have the opportunity to improve care and reduce costs simultaneously. In the next five to ten years, there will be long-term, randomized, controlled trials evaluating the newer agents. Whether their improved metabolic profiles result in better morbidity and mortality over diuretics and β-blockers remains to be proved.

REFERENCES

1. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1993; 153:154-183

2. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988; 148:1023-1038

3. Carruthers SG, Larochelle P, Haynes RB, Patrasovits A, Schiffrin EL: Report of the Canadian Hypertension Society Consensus Conference—1. Introduction. Can Med Assoc J 1993; 149:289-293

4. Sever P, Beevers G, Bulpitt C, et al: Management guidelines in essential hypertension: Report of the second working party of the British Hypertension Society. BMJ 1993; 306:983-987

5. Collins R, Peto R, MacMahon S, et al: Epidemiology: Blood pressure, stroke, and coronary heart disease—Pt 2, Short-term reductions in blood pressure: Overview of randomised drug trials in their epidemiological context. Lancet 1990; 335:827-838

6. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension—Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265:3255-3264

7. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO: Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension—STOP-Hypertension. Lancet 1991; 338:1281-1285

8. MRC Working Party: Medical Research Council trial of treatment of hypertension in older adults: Principal results. BMJ 1992; 304:405-412

9. Hebert PR, Moser M, Mayer J, Glynn RJ, Hennekens CH: Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. Arch Intern Med 1993; 153:578-581

10. Insua JT, Sacks HS, Lau TS, et al: Drug treatment of hypertension in the elderly: A meta-analysis. Ann Intern Med 1994; 121:355-362

11. Psaty BM, Savage PJ, Tell GS, et al: Temporal patterns of antihypertensive medication use among elderly patients—The Cardiovascular Health Study. JAMA 1993; 270:1837-1841

12. Aucott JN, Taylor AL, Wright JT Jr, et al: Developing guidelines for local use: Algorithms for cost-efficient outpatient management of cardiovascular disorders in a VA medical center. Jt Comm J Qual Improv 1994; 20:17-32

13. Wiklund I: Quality of life and cost-effectiveness in the treatment of hypertension. J Clin Pharm Ther 1994; 19:81-87

14. McCorvey E Jr, Wright JT Jr, Culbert JP, McKenney JM, Proctor JD, Annett MP: Effect of hydrochlorothiazide, enalapril, and propranolol on quality of life and cognitive and motor function in hypertensive patients. Clin Pharm 1993; 12:300-305

15. Neaton JD, Grimm RH Jr, Prineas RJ, et al: Treatment of mild hypertension study—Final results. JAMA 1993; 270:713-724

16. Wassertheil-Smoller S, Blaufox MD, Oberman A, et al: Effect of antihypertensives on sexual function and quality of life: The TAIM study. Ann Intern Med 1991; 114:613-620

17. Prisant LM, Carr AA, Bottini PB, Solursh DS, Solursh LP: Sexual dysfunction with antihypertensive drugs. Arch Intern Med 1994; 154:730-736

18. Materson BJ, Reda DJ, Cushman WC, et al: Single-drug therapy for hypertension in men—A comparison of six antihypertensive agents with placebo in The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. N Engl J Med 1993; 328:914-921

19. Moser M: Can the cost of care be contained and quality of care maintained in the management of hypertension? Arch Intern Med 1994; 154:1665-1672

20. Torvik D, Madsbu H: An open one-year comparison of doxazosin and prazosin for mild to moderate essential hypertension. Am J Cardiol 1987; 59:68G-72G

21. Warram JH, Laffel LM, Valsania P, Christlieb AR, Krolewski AS: Excess mortality associated with diuretic therapy in diabetes mellitus. Arch Intern Med 1991; 151:1350-1356

22. Dawson KG, McKenzie JK, Ross SA, Chiasson JL, Hamet P: Report of the Canadian Hypertension Society Consensus Conference: 5. Hypertension and diabetes. Can Med Assoc J 1993; 149:821-826

23. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J: Antihypertensive drug therapy and the initiation of treatment for diabetes mellitus. Ann Intern Med 1992; 118:273-278

24. Systolic Hypertension in the Elderly Program Cooperative Research Group: Implications of the Systolic Hypertension in the Elderly Program. Hypertension 1993; 21:335-343

25. Fuller JH: Hypertension and diabetes—Epidemiologic aspects as a guide to management. J Cardiovasc Pharmacol 1993; 21(suppl 2):S63-S66

26. Slataper R, Vicknair N, Sadler R, Bakris GL: Comparative effects of different antihypertensive treatments on progression of diabetic renal disease. Arch Intern Med 1993; 153:973-980

27. Lacourcière Y, Nadeau A, Poirier L, Tancrède G: Captopril or conventional therapy in hypertensive type II diabetics—Three-year analysis. Hypertension 1993; 21(pt 1):786-794

28. Hoes AW, Grobbee DE, Peet TM, Lubsen J: Do non-potassium-sparing diuretics increase the risk of sudden cardiac death in hypertensive patients?—Recent evidence. Drugs 1994; 47:711-733

29. Siscovick DS, Raghunathan TE, Psaty BM, et al: Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 1994; 330:1852-1857

30. Frohlich ED, Apstein C, Chobanian AV, et al: The heart in hypertension. N Engl J Med 1992; 327:998-1008

31. Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G: Primary prevention with metoprolol in patients with hypertension. JAMA 1988; 259:1976-1982

32. Hannedouche T, Landais P, Goldfarb B, et al: Randomized controlled trial of enalapril and beta blockers in non-diabetic chronic renal failure. BMJ 1994; 309:833-837

33. Edelson JT, Weinstein MC, Tosteson AN, Williams L, Lee TH, Goldman L: Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. JAMA 1990; 263:407-413

34. Hilleman DE, Mohiuddin SM, Lucas BD Jr, Stading JA, Stoysich AM, Ryschon K: Cost-minimization analysis of initial antihypertensive therapy in patients with mild-to-moderate essential diastolic hypertension. Clin Ther 1994; 16:88-102

35. Fletcher AE, Bulpitt CJ: How far should blood pressure be lowered? N Engl J Med 1994; 326:251-254

36. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR: The J-curve phenomenon and the treatment of hypertension—Is there a point beyond which pressure reduction is dangerous? JAMA 1991; 265:489-495

Articles

Alpine Skiing Injuries

A Nine-Year Study

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Injury patterns in alpine skiing have changed over time as ski, boot, binding, and slope-grooming technologies have evolved. We retrospectively examined injury patterns in alpine skiers over a 9-year period at the Mammoth and June mountains (California) ski area. A total of 24,340 injuries were reported for the 9 seasons studied, and total lift tickets sold numbered 9,201,486. The overall injury rate was 2.6 injuries per 1,000 skier days and increased slowly over the period studied. The knee was the most frequently injured area at 35% of all injuries. Increasing trends ($P < .05$) were noted for the rates of lower extremity injuries (37%) and knee injuries (45%). A decreasing trend was noted for the rate of lacerations (31% decrease). Slight increases were noted in upper extremity and axial injury rates. Skiing injuries continue to be a worrisome recreational problem despite improvements in ski equipment and slope-grooming techniques. The increasing trend in lower extremity, particularly knee, injury rates highlights the need for continued skier education and equipment innovation.

(Davidson TM, Laliotis AT: Alpine skiing injuries—A nine-year study. West J Med 1996; 164:310-314)

The sport of alpine skiing has grown dramatically in the United States from an estimated 10,000 participants in 1935 to 14.5 million in 1987.[1] Injury rates and patterns have been extensively studied both in this country and abroad and have shown a significant decrease from the range of 7.6 to 10.9 injuries per 1,000 skier days[2,3] in the late 1950s and 1960s to current estimates of 0.9 to 6.0 injuries per 1,000 skier days.[4-8] It is suggested that changes in ski equipment (skis, bindings, boots, and poles) and modern slope-grooming techniques have led to this reduction in the overall injury rate,[7] specifically leading to reduced injury rates for ankle sprains, ankle fractures, and spiral tibial fractures.[1-3,5,6,8-11]

Certain injury types have not shown reductions, however, with injuries to knee ligaments being the most important exception. The knee has been reported as the most common site of injury, accounting for 20% to 27% of all skiing injuries ("Bringing Skiers to Their Knees," *Snow Country*, 1993 March-April, pp 70-74).[1,4,7,8,10-13] The incidence of knee injuries has shown little or no decrease through the years,[2,5,6,8] and a recent study from Australia reported an increasing incidence of knee injuries.[3] Over the past 30 years, little change has been noted in upper extremity injury rates, including the skier's thumb.[2,3,5,6,8,14-17]

In this study, we examine ski injury patterns at a major western ski resort over a nine-year period (1983 to 1992).

Patients and Methods

Mammoth-June, in the eastern Sierra mountains of California, is one of the largest ski resort areas in North America. The ski patrol first-aid rooms at the base of each mountain provide first-aid care and triage for all skiers injured at both resorts. Since the 1983-1984 winter season at Mammoth and the 1986-1987 season at June, injuries reported by the ski patrol and first-aid room staff have been recorded on a computer database. Accident information recorded by the patrol includes injury zone, injury type, and general information such as age, sex, and skier ability. One of us (T.M.D.) has been a member of the Mammoth-June Ski Patrol since 1963 and participated in the study design and data analysis. Physician evaluation is not available on site. Skiers self-triage to several sites, and physicians' diagnoses are not available.

We examined the incident-report database from Mammoth-June for all recorded skiing injuries from the 1983-1984 through the 1991-1992 winter seasons. Specific injury rates were calculated by dividing the number of injuries for a particular season by the number of skier days in that season and multiplying by 1,000. This yields the standard method of reporting skiing injury rates: injuries per 1,000 skier days. Skier days are represented by lift ticket sales at the resort, with one ticket equaling one skier day. We can anticipate a small underestimation error in this calculation because skiers with employee or season passes are not counted in the total skier days. Conversely, snowboarders were excluded from the count of injured skiers and may represent as many as 5% of lift ticket sales beginning with the 1989-1990 season when they were first invited to the Mammoth Mountain Ski Area.

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TABLE 1.—*Demographics of Skiers Injured at Mammoth-June (California) Ski Resorts Over a 9-Year Period*

Characteristic	*1983 to 1992*
Total injuries, No.	24,340
Mean age (SD), years	27.9 (13.5)
Sex	
Male, %	50
Female, %	50
Ability	
Beginner, %	19
Low intermediate, %	13
Intermediate, %	43
Advanced, %	18
Expert, %	4
Racer, %	2

SD = standard deviation

Statistical analysis was performed by linear regression. The level of significance to reject the null hypothesis was set at less than .05.

Results

Demographics

From 1983-1984 through 1991-1992, a total of 24,340 injuries were reported by the Mammoth-June Ski Patrol. During this same time period, 9,201,486 lift tickets were sold. Table 1 presents the mean age, sex, and ability levels of those injured over the nine-year period. There were no significant trends for sex or ability level over the nine years. Figure 1 shows that the age of those injured increased 11% over the nine-year period (26.5 years to 30.25 years, $R^2 = .83$, $P < .01$).

Trends in Overall Injury Rate

The overall injury rate over the nine-year period, shown in Figure 2, was 2.6 injuries per 1,000 skier days. The overall injury rate increased 59%, from 1.9 injuries per 1,000 skier days in 1983-1984 to 3.0 in 1991-1992 ($R^2 = .76$, $P < .01$).

Most Frequent Injury Zones

Lower extremity injuries accounted for 54% of all injuries. Injuries involving the axial skeleton (head, neck, chest, back, trunk, and pelvis) accounted for 21% of all injuries, and upper extremity injuries represented 19% of all injuries.

The area most frequently injured was the knee, accounting for 35% of all injuries. The next most frequently injured area was the head and face at 15%. Shoulder injuries were the most common upper extremity injury at 8%. Thumb injuries were the second most common upper extremity injury at 4%. The number of injuries for each injury zone is shown in Table 2.

Trends in Injury Rate for Specific Regions

Upper extremity injuries showed a significant increase in the rate of 53% from 0.38 injuries to 0.54 injuries per 1,000 skier days over the nine years ($R^2 = .46$, $P < .05$) (Table 3). Within the subset of upper extremity injuries, thumb and wrist injury rates both increased (66%, $R^2 = .45$, $P < .05$, and 94%, $R^2 = .57$, $P < .05$, respectively).

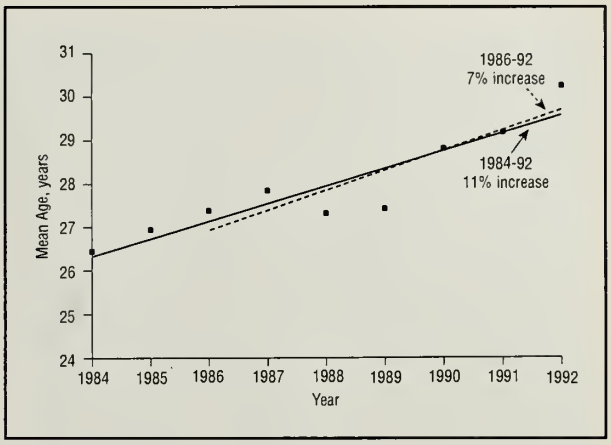

Figure 1.—The graph shows the mean age versus the year of the study. Linear regression lines for the 9-year period are shown. A significant increase of 11% ($R^2 = .83$, $P < .01$) in the mean age of injured skiers was noted.

Axial skeleton injuries showed a similar pattern, with the total number of axial skeleton injuries—head, clavicle, chest, rib, back, and pelvis—all showing significant ($P < .05$) increases for the nine-year period.

The total number of lower extremity injuries showed a significant increasing trend (60% increase, $R^2 = .86$, $P < .01$). Over the nine-year period, the number of knee injuries showed a 92% increase ($R^2 = .88$, $P < .01$). The rates for sprains and fractures are shown in Figure 3.

Ability Level and Knee Sprains

We compared the ability level with the incidence of knee sprains. Skiers who classified themselves as beginners or low intermediates sustained 25% and 18%, respectively, of the total number of knee sprains, while only sustaining 19% and 13%, respectively, of the total number of injuries. Intermediate skiers received 41% of all knee sprains and 42% of all injuries. Skiers who

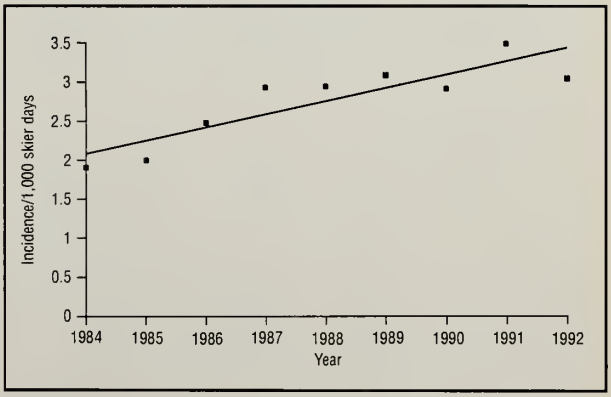

Figure 2.—The trend in the overall injury rate is shown. Over the 9-year period of the study, linear regression analysis showed a significant increase in the overall injury rate of 59% ($R^2 = .76$, $P < .01$).

TABLE 2.—*Number of Injuries for All Injury Zones, 1983 to 1992*

Injury Zone	*1983-1984*	*1984-1985*	*1985-1986*	*1986-1987*	*1987-1988*	*1988-1989*	*1989-1990*	*1990-1991*	*1991-1992*	*Total*
Upper extremity										
Shoulder	219	184	276	165	297	259	222	97	196	1,915
Arm	76	56	95	70	63	73	61	31	76	601
Elbow	27	13	31	14	28	17	13	4	14	161
Wrist	43	42	68	34	84	73	64	34	49	491
Hand	46	48	83	49	59	46	31	23	27	412
Thumb	87	93	173	111	118	129	120	96	116	1,043
Subtotal	498	436	726	443	649	597	511	285	478	4,623
Lower extremity										
Hip	20	37	50	33	46	49	36	15	39	325
Thigh	69	53	62	32	70	47	2	4	8	347
Knee	771	777	1,127	660	1,046	1,142	1,037	588	1,008	8,156
Leg	262	306	316	176	246	291	246	129	252	2,224
Ankle	223	155	194	106	205	172	141	77	168	1,441
Foot	10	8	13	9	7	11	3	2	2	65
Subtotal	1,355	1,336	1,762	1,016	1,620	1,712	1,465	815	1,477	12,558
Head	249	233	292	194	267	260	306	135	251	2,187
Spine										
Neck	21	24	40	34	46	43	26	13	33	280
Back	70	63	74	60	99	74	73	53	80	646
Pelvis	1	2	1	1	2	3	2	1	5	18
Subtotal	92	89	115	95	147	120	101	67	118	944
Other										
Clavicle	4	24	23	11	20	28	15	14	32	171
Face	178	139	280	144	252	205	137	84	98	1,517
Internal	63	107	157	111	166	169	138	58	126	1,095
Rib	27	29	42	16	35	49	42	22	26	288
Chest	1	8	8	4	7	9	7	6	7	57
Teeth	1	4	7	2	8	0	1	2	2	27
Multiple	10	74	185	39	85	61	104	25	40	623
Other	22	24	18	18	19	44	35	23	47	250
Subtotal	306	409	720	345	592	565	479	234	378	4,028
Total	2,500	2,503	3,615	2,093	3,275	3,254	2,862	1,536	2,702	24,340

rated themselves as advanced and above sustained 16% of knee sprains and 24% of all injuries. We have no information about the ability levels of those who were not injured.

Discussion

The overall injury rate for the nine years, 2.7 injuries per 1,000 skier days, is consistent with rates found in the United States, Australia, and Europe.[2-8] Unlike previous studies that show a decreasing trend in the overall injury rate,[2,3,5,6,8] we found a small increase over the nine-year period.

The overall injury rate and the three subsets of axial, lower extremity, and upper extremity injuries all had rates that increased significantly over the nine years of the study from 1983-1984 through 1991-1992. The reasons this might occur include an increased number of beginning skiers, poorer physical conditioning, improved slope grooming with a resultant firmer snow surface, more skiers leading to crowding on the ski slopes, and increasing skiers' age. There are also reasons to predict decreasing accident rates, specifically improvements in equipment, binding-adjustment practices, and slope-grooming practices; the presence of wider and safer slopes; and an increase in ski school availability and instruction.

The increased injury rate, although statistically significant, is small and may be explained by several factors. With improved risk management practices, there is a trend to report virtually all skier-patrol encounters, so that even mild "ski yourself down the hill" injuries are more likely to have an accident report completed. A new first-aid program called Winter Emergency Care sponsored by the National Ski Patrol Association replaced the National Red Cross's Advanced First-Aid Program in 1988. With increasing knowledge and improved evaluation skills, ski patrol staff are more likely to make and record suspected diagnoses. In today's litigious world, the thresholds for diagnosis and first-aid treatment are raised.

The study is certainly flawed by the lack of physician diagnosis. The patrollers are well trained but, lacking x-ray films and physician examination skills, are required to "overdiagnose." If a skier falls and complains of knee pain sufficient to require a leg splint and a toboggan ride off the ski slope, the patrol staff diagnoses a presumed knee sprain. The severity of the injury is not graded. If a skier falls and injures the midportion of the lower leg, the patrol staff diagnoses a presumed lower leg fracture.

It is the senior author's opinion that the site of injury is correctly diagnosed 100% of the time. Because all

TABLE 3.—*Trends in Injury Rates for All Injury Zones Using Linear Regression Analysis for the Full 9-Year Study Period*

*Injury Rate**	*Linear Regression Statistics†*			
Injury Zone	*1983*	*1992*	*% Change*	R^2
Overall	1.91	3.04	64	0.76‡
Upper extremity				
Shoulder	0.62	0.22	39	0.39
Arm	0.06	0.09	35	0.19
Elbow	0.02	0.02	−29	0.14
Wrist	0.03	0.06	99	0.57§
Hand	0.04	0.03	−15	0.04
Thumb	0.07	0.13	115	0.45§
Total	0.38	0.54	48	0.46§
Lower extremity				
Hip	0.02	0.04	64	0.37
Thigh	0.05	0.01	−82	0.55§
Knee	0.89	1.13	111	0.88‡
Leg	0.20	0.28	36	0.68‡
Ankle	0.17	0.19	25	0.27
Foot	0.01	0.00	−57	0.30
Total	1.04	1.66	71	0.86‡
Axial skeleton				
Head	0.19	0.28	66	0.76‡
Face	0.14	0.11	2	0
Teeth	0.001	0.002	−2	0
Neck	0.02	0.04	57	0.21
Clavicle	0.00	0.04	294	0.68‡
Chest	0.001	0.008	242	0.58§
Rib	0.02	0.03	102	0.48§
Back	0.05	0.09	104	0.60§
Pelvis	0.001	0.006	835	0.62§
Total	0.42	0.60	54	0.59§
Other				
Multiple injuries	0.01	0.04	23	0.02
Internal injuries	0.05	0.14	90	0.51§
Other	0.02	0.05	411	0.79‡

*Injury rate is presented as number of injuries per 1,000 skier days.
†Linear regression was performed for the full 9-year period, with the percentage of change calculated from regression estimates.
‡$P < .01$.
§$P < .05$.

injuries require the more serious diagnoses to avoid the legal risk of misdiagnosis and mistreatment, the severity of an injury is always conservatively graded. Extremity injuries are accurately diagnosed. Spine injuries are always diagnosed if any suspicion of injury exists.

The raw data show a statistically significant (albeit small) increase in skiing accident rates. Viewed from a larger perspective, the skiing accident rate in this large study is between 2.0 and 3.0 accidents per 1,000 skier days. Based on these facts, we suggest that the overall injury rate for alpine skiers at Mammoth-June in the late 1980s and early 1990s is around 2.6 to 3.0 per 1,000 skier days, a finding that has been echoed recently at an Australian resort.[3] This suggests that despite improvements in slope grooming and snowmaking at Mammoth-June resorts, as well as changes in ski equipment technology, no reduction in overall skier injury rate has been noted in the period from 1983 to 1992.

Perhaps the most worrisome observation in this study is the upward trend in the incidence of lower extremity injuries. Unlike the findings in other reports of decreasing trends in the incidence of lower extremity injuries,[2,3,5,6,8] there was a significant increase in the number of lower extremity injuries over the nine years of the study. Johnson has clearly shown in several studies that the incidence of injuries to the lower extremity caused by twisting moments—using the *Random House Dictionary* definition of "moment" as a tendency to produce motion especially about an axis—have substantially decreased over the years due to improvements in binding design and a higher percentage of properly set binding-release torques.[1,5,6,8] Johnson and others have also reported that the incidence of knee injuries has not decreased substantially over the past 30 years.[1,6,8] One worker has recently shown an increasing rate of injuries caused by bending moments in the lower extremity.[3] Similar results were noted in this study, with the rate of injuries to feet and ankles showing no increase or a decrease, whereas the incidence of knee injuries increased. This points to what others have suggested, namely that ski equipment design has effectively evolved to protect against the classic skiing injuries: spiral fractures of the tibia and fractures and sprains in the ankle, while having less success at reducing bending and twisting forces farther up the leg.[2,3,5,9-11] Alternatively, with the ankles and lower legs better protected, injuries may be transferred to the next most vulnerable area, namely the knees.

Others have noted that whereas the rate of most skiing injuries is declining, the rate of knee injuries has either remained unchanged since as far back as the 1960s or has increased.[1,2,5,6,8] It has been suggested that these findings are related to both greater boot-top height, which transfers bending and twisting forces upward to the knees, and a lack of binding designs that respond to the bending and torsional forces that are transferred to the knees (*Snow Country* 1993 March-April, pp 70-74).[1-3,5,9-11] This study supports these findings.

The incidence of thumb injuries showed a slight but significantly increasing trend in this study. This agrees with previous findings that it remains the site of the first or second most common upper extremity injury.[2,3,5-8] The mechanism of injury for the most common hand injury,

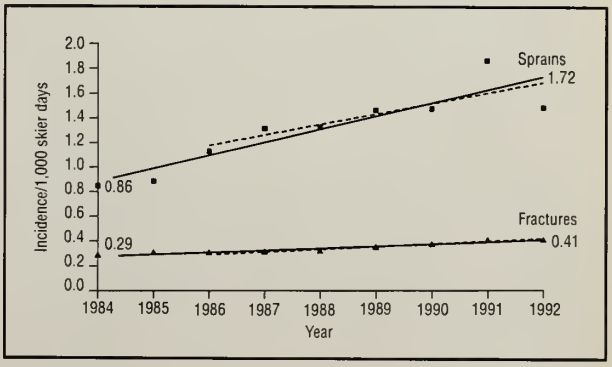

Figure 3.—Trends in the rates of sprains and fractures are shown. The fracture rate is stable. The rate of sprains (predominantly of knees) is rising and presumably accounts for much of today's skiing injury rates.

"skier's thumb," involves a fall with the abducted thumb hitting the snow while the ski pole grip acts as a lever to stretch or tear the ulnar collateral ligament.[14,15] Changes in the design of ski pole handles, including the strapless pole, have not lessened the rate of injury and in some instances have been shown to increase the risk of injury.[16,17] Further investigation into skier's thumb injuries and ski pole design is needed.

The decrease in the number of lacerations over the study period coincides with the use of ski brakes and the discontinuation of safety straps. Presumably falling skiers, without safety straps, are less likely to strike and be cut by their own skis. This decrease in the rate of lacerations has been reported by others.[3,6]

A curious finding in this study relates to the increasing age of injured alpine skiers. This increase was most pronounced for the final four years of the study, when the mean age of those injured went from 27.4 years during the 1988-1989 season to 30.2 years during the 1991-1992 season, an increase of greater than 2% per year. Because we do not know the demographics of all who purchase ski tickets, we can only speculate that this change relates to the introduction of snowboarding at Mammoth Mountain. Snowboarders were first invited during the 1988-1989 season and have grown to account for an estimated 5% of the slope users by the end of the 1991-1992 season. Snowboarder participants are younger and have been shown to have a lower mean age of injured participants than alpine skiers.[18-20] Thus, we believe that the trend of increasing age of injured alpine skiers may reflect the growing popularity of snowboarding among younger participants who have turned from skiing to snowboarding or that skiers really are increasing in age, perhaps because fewer children or young adults are skiing. We favor the snowboard explanation.

REFERENCES

1. Johnson RJ: Skiing and snowboarding injuries—When schussing is a pain. Postgrad Med 1990; 88:36-38, 43-45, 49-51

2. Tapper EM: Ski injuries from 1939 to 1976: The Sun Valley experience. Am J Sports Med 1978; 6:114-121

3. Sherry E, Fenelon L: Trends in skiing injury type and rates in Australia—A review of 22,261 injuries over 27 years in the Snowy Mountains. Med J Aust 1991; 155:513-515

4. Lystad H: A five year survey of skiing injuries in Hemsedal, Norway, *In* Johnson RJ, Mote CD Jr, Binet MH (Eds): Skiing Trauma and Safety: Seventh International Symposium. Philadelphia, Pa, American Society for Testing and Materials, 1989, pp 32-40

5. Johnson RJ, Ettlinger CF, Campbell RJ, Pope MH: Trends in skiing injuries—Analysis of a 6-year study (1972 to 1978). Am J Sports Med 1980; 8: 106-113

6. Johnson RJ, Ettlinger CJ: Alpine ski injuries: Changes through the years. Clin Sports Med 1982; 1:181-197

7. Sherry E: Skiing injuries in Australia. Med J Aust 1984; 140:530-531

8. Johnson RJ, Ettlinger CF, Shealy JE: Skier injury trends, *In* Johnson RJ, Mote CD Jr, Binet MH (Eds): Skiing Trauma and Safety: Seventh International Symposium. Philadelphia, Pa, American Society for Testing and Materials, 1989, pp 25-31

9. Trevino SG, Alvarez R: The spectrum of lower leg injuries in skiing. Clin Sports Med 1982; 1:263-276

10. Howe J, Johnson RJ: Knee injuries in skiing. Clin Sports Med 1982; 1:277-289

11. Robinson M: Hazards of alpine sport. Aust Fam Physician 1991; 20: 961-970

12. Ekeland A, Holtmoen A, Lystad H: Lower extremity equipment-related injuries in alpine recreational skiers. Am J Sports Med 1993; 21:201-205

13. Ekeland A, Holtmoen A, Lystad H: Skiing injuries in alpine recreational skiers, *In* Johnson RJ, Mote CD Jr, Binet MH (Eds): Skiing Trauma and Safety: Seventh International Symposium. Philadelphia, Pa, American Society for Testing and Materials, 1989, pp 41-50

14. Morgan JV, Davis PH: Upper extremity injuries in skiing. Clin Sports Med 1982; 1:295-309

15. Elliott BG, Sherry E: Common snow skiing injuries. Aust Fam Physician 1984; 13:570-574

16. Primiano GA: Skiers' thumb injuries associated with flared ski pole handles. Am J Sports Med 1985; 13:425-427

17. Van Dommelen BA, Zvirbulis RA: Upper extremity injuries in snow skiers. Am J Sports Med 1989; 17:751-753

18. Ganong RB, Heneveld EH, Beranek SR, et al: Snowboarding injuries: A report on 415 patients. Physician Sports Med 1992; 20:114-122

19. Abu-Laban RB: Snowboarding injuries: An analysis and comparison with alpine skiing injuries. Can Med Assoc J 1991; 145:1097-1103

20. Davidson TM, Laliotis AT: Snowboarding injuries—A four-year study with comparison with alpine ski injuries. West J Med 1996; 164:231-237

Articles

Preeclampsia
Still an Enigma

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This paper was chosen as the winner of THE WESTERN JOURNAL OF MEDICINE'*s 1995 Medical Student Writing Competition. The contest was open to all students attending medical schools in the West and is repeated annually.*

LINDA HAWES CLEVER, MD
Editor

In pregnancy, drowsiness with headache accompanied by heaviness and convulsions is generally bad.

Coan Prognosis, XXXI, #507
BEFORE 4TH CENTURY BC[1]

Preeclampsia is a disorder specific to pregnancy that is recognized clinically by the triad of hypertension, proteinuria, and edema. It can, in some cases, progress to seizures (known as eclampsia), coma, and death.[2] Even when not progressing to outright eclampsia, preeclampsia can lead to such complications as renal failure,[3] hepatic rupture,[4] intracranial bleeding,[2] intrauterine growth retardation,[5] and intrauterine fetal death.[2] It was first described as a separate clinical disorder in the mid-18th century in France[6] and remains to this day the single most common cause of maternal and fetal morbidity and mortality worldwide.[7,8] Its incidence in developed countries is estimated to be 5% to 10%,[9] and in the United States, it complicates fully 10% to 12% of the 3.5 million pregnancies a year.[10]

Preeclampsia is an elusive disease from both a clinical and a pathophysiologic standpoint. Clinically, although a strict set of criteria define preeclampsia, many cases of eclampsia occur without the patients ever manifesting one or more symptoms of the definitional triad.[11] Conversely, some patients who receive the initial diagnosis of preeclampsia later prove to have chronic disorders that came to light during pregnancy but are not gestationally related, thus precluding the diagnosis of preeclampsia. So the best clinical criteria lack both the sensitivity and the specificity needed for making the diagnosis of so dangerous a condition.

In terms of pathophysiology, despite decades of intensive research and the diligent application of some of the most sophisticated cellular and molecular biologic research tools in use today, the initiating events in preeclampsia defy description. Further, although new information concerning the many physiologic derangements associated with this disorder is emerging almost daily,* the condition's elusiveness in the laboratory has led to a lack of treatment options in clinics and on hospital wards. The only definitive treatment currently available for this pregnancy-specific disease is to terminate the pregnancy. Delivery, specifically delivery of the placenta, brings about a resolution of symptoms within days to weeks, and the risk of eclamptic seizures drops off sharply at 48 hours postpartum.

Pathophysiology of Preeclampsia or Eclampsia

Placenta

The uterine spiral arteries arise from the basal arteries and travel through the myometrium to the decidual layer of the uterus. In pregnancy, they dilate to meet the increasing metabolic demands of the growing fetoplacental unit. In normal pregnancy, fetal trophoblastic cells invade these spiral arteries to about the first third of the myometrial segment.[6] This invasion occurs in two separate waves and is usually completed between 16 and 22 weeks of gestation.[12] In the arterial segments that have been successfully invaded, the endothelium is entirely replaced by the invading trophoblastic cells, and the musculoelastic media is replaced by trophoblast and fibrin.[13] In addition to accomplishing arterial dilatation, the endothelial replacement by trophoblastic cells eliminates endothelial cell surface receptors and renders the arteries unresponsive to circulating pressors.[14] This process has the overall effect of establishing the placental circulation as a low-pressure sink for maternal blood flow.

In preeclampsia, there is an observed failure of trophoblastic invasion into the maternal spiral arteries.[13] A recent comparison of placental bed spiral arteries from women with a normal pregnancy and those with severe

*See also the editorial by R. N. Taylor, MD, PhD, "Lightning and Fattening—Evolving Concepts in the Pathogenesis of Preeclampsia," on pages 359-361 of this issue.

(Duda J: Preeclampsia—Still an enigma. West J Med 1996; 164:315-320)

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ABBREVIATIONS USED IN TEXT

CLASP = Collaborative Low-Dose Aspirin Study in Pregnancy
EDRF = endothelium-derived relaxing factor
HELLP [syndrome] = hemolysis, elevated liver enzyme levels, and low platelet count
NIH = National Institutes of Health

preeclampsia found complete invasion and trophoblastic replacement in 100% of the decidual segments and 76% of the myometrial segments of spiral arteries studied from normal pregnancies, with 44% and 18% complete invasion in the same respective layers in patients with preeclampsia.[15] Accordingly, the average diameter of spiral arteries in women with preeclamptic pregnancies is greatly reduced from that in women with normal pregnancies. Additional changes have been observed and termed "acute atherosis." These changes were first described in 1950 as "acute arterionecrosis with intramural infiltration by foam cells"[16] and are seen exclusively in the decidual and myometrial segments of the spiral arteries. The severity of the lesions and the extent of involvement of the placental bed correlate well with the clinical severity of the disease.[6] Together these changes severely limit placental blood flow and maintain the responsiveness of the spiral arteries to circulating vasodilating and, importantly, vasospastic elements.

In the prevailing theory of preeclamptic pathogenesis, two major conceptual links have yet to be substantiated. Although the placenta is now generally accepted to be central in preeclampsia, evidence elucidating the events immediately preceding the placental lesion and those immediately following is lacking. The events immediately following the placental lesion are thought to derive from ischemic placenta and to lead to the generalized endothelial dysfunction for which evidence continues to accumulate. The events immediately preceding the placental lesion address the question of the underlying process responsible for this morbid obstetric complication. Both links are currently postulated to be immune in nature.

Immune System

Although preeclampsia does occur in multiparous patients,[17] epidemiologic data show it to be primarily a disease of first pregnancy.[18] There are also data that suggest a higher risk of occurrence when there has been a recent change in sexual partner,[19] and at least one study shows that there is an increased risk with couples who have used barrier contraceptive methods before conception.[20] These and other studies make up the epidemiologic evidence for the primary immunologic maladaptation that is postulated as the initiating event in preeclampsia.[21-25]

To some extent, investigations into the proposed immunologic dysfunction involved in preeclampsia are limited by a lack of understanding of the important immunologic events by which the maternal immune system builds tolerance to the fetal allograft in normal pregnancy. Currently it is thought that the default behavior of maternal immune rejection of her conceptus is prevented by immune-blocking activity of unknown cause.[26] Maternal-paternal HLA-antigen sharing is a possible mechanism by which the maternal immune-blocking system fails to activate.[27-30] The thought is that the signal for activation of the blocking system arises from the initial stimulation of the maternal immune system by the paternal antigens carried on fetal trophoblastic cells. In cases where there is a substantial amount of maternal-paternal HLA-antigen sharing, the initial maternal immune stimulation may be insufficient to activate the blocking system, leaving the maternal immune response intact to limit trophoblastic invasion. This theory predicts an increased incidence of preeclampsia in couples who share HLA antigens, and indeed some investigators have noted this association.[31-33] Others, however, have not.[34]

There has been some attempt to link preeclampsia to specific HLA antigens, but here, too, the data are inconclusive. In 1990 an increased incidence of preeclampsia with maternal-fetal sharing of HLA-DR4 was found,[35] but other studies have since found the incidence to be the same[36] or decreased.[37] In 1992, HLA-DR associations with respect to immunologic symmetry between mother and conceptus were studied.[36] An increased incidence of preeclampsia was found in patients in whom the fetus did not have HLA-DR antigens allogeneic to its mother, but the mother had an HLA-DR antigen allogeneic to her fetus. In 1994, in a prospective observational study of 712 primigravid women, a threefold to fourfold increase was found in the risk of preeclampsia and intrauterine growth retardation in women with an extended haplotype of A23/29, B44, DR7.[38] It is difficult to determine the consistency of these data with those of others because the authors did not report the haplotypes of the fetuses studied. As yet, no specific HLA haplotype has been definitively shown to increase the risk of preeclampsia developing, and no particular pattern of HLA sharing between mother, father, and fetus has been found in patients with preeclampsia.

Once formed, the placental lesion is thought to generate toxins that cause generalized maternal endothelial dysfunction. In a review article, it was suggested that the increased production of oxygen-free radicals and lipid peroxides (a commonly accepted event) may be the missing link between the placenta and the endothelium.[39] The authors advocated the view of the decidua as a lymphoid organ and noted that free radicals may be liberated in a local immune response against fetal trophoblasts. These high-energy ions combine easily with other molecules, notably those present in blood circulating through the placenta. These free-radical oxidative products, of which lipid peroxides are presumed to be one type, are then carried to the general maternal circulation where they are known to cause many of the biochemical imbalances seen in preeclampsia. Free radicals and their oxidative products can lead to decreased levels of endothelium-derived relaxing factor (EDRF),

increased levels of endothelin, decreased levels of prostacyclin, and increased levels of thromboxane.[40-43]

Endothelium

Vascular endothelium has long been known to serve many functions beyond its structural role. Situated between the vascular smooth muscle layer and the complex and ever-changing milieu of the circulation, it is both the translator through which circulating signals affect vascular tone and the barrier that protects against spontaneous clot formation and vascular leakage. Vasoconstricting factors, such as endothelin, angiotensin II, and thromboxane, and vasodilating substances, including EDRF and prostacyclin, all must act through an intact endothelium. Moreover, the integrity of the tight junctions between endothelial cells prevents fluid leakage and the exposure of coagulating factors to the procoagulant basement membrane. Endothelial dysfunction, then, can have disastrous consequences for these important homeostatic systems.

End-organ disease has been studied for years and is well characterized, especially in the brain, liver, and kidneys. The brains of eclamptic women show many foci of ischemic and hemorrhagic necrosis.[6] Their livers show periportal hemorrhage and sinusoidal fibrin and fibrinogen deposition.[4] A recent report of a patient with recurrent preeclamptic hepatic hemorrhage describes the development of hepatic artery aneurysms, presumably due to hypertension.[44] Other studies support the idea of hepatic artery hypertension by documenting increased hepatic artery pulsatility in patients with both preeclampsia alone and preeclampsia with the syndrome of *h*emolysis, *e*levated *l*iver enzyme levels, and a *l*ow *p*latelet count (HELLP), a syndrome indicative of severe preeclampsia.[45] The characteristic renal lesion, called "glomeruloendotheliosis," is described as "diffusely enlarged, bloodless glomeruli"[3(p446)] with fibrin deposition and increased numbers of mesangial and endothelial cells. These multiorgan lesions are all consistent with endothelial dysfunction leading to vasospasm (with ischemia, hypertension, and hemorrhage); organ-specific, compensated, disseminated intravascular coagulation (with diffuse fibrin deposition); and decreased EDRF production (with increased platelet-derived growth factor production and endothelial proliferation).

Further evidence in support of the occurrence of vasospasm in preeclampsia is found in the earliest detectable changes in women in whom the disorder develops. In normal pregnancy, the action of progesterone on vascular smooth muscle results in generalized vasodilation and an associated drop in blood pressure.[46] Blood volume is expanded, and renal blood flow and the glomerular filtration rate increase.[12] Despite this, due in part to an increased availability of renin precursors,[46,47] the renin-angiotensin-aldosterone system is stimulated, and vascular sensitivity to angiotensin II decreases.[48,49] In preeclampsia, after initially achieving resistance to angiotensin, endothelium regains its sensitivity, and as gestation progresses, patients become increasingly sensitive until they surpass the sensitivity of nonpregnant patients.[46,48,50] This angiotensin sensitivity is particularly dangerous in a patient with increased circulating angiotensin levels in pregnancy. These circulating levels prove to be somewhat responsive to the increased endovascular angiotensin sensitivity and are found to be decreased in preeclampsia when compared with normal pregnancy. They are unable to fully compensate, however, and remain substantially above nonpregnant levels.[46]

In addition to their sensitivity to angiotensin, preeclamptic patients have been found to be more sensitive to all pressors tested than women with normal pregnancies.[51] These pressors include catecholemines[50] and pituitary extracts (presumed vasopressin).[52] It has been proposed by some that the general endothelial pressor sensitivity may be due to the prostacyclin-thromboxane imbalance seen in patients with preeclampsia.[39] The ratio of prostacyclin (secreted by the intact endothelium) to thromboxane (made primarily by activated platelets) may be the major compensatory mechanism protecting against generalized vasospasm. If this is the case, then damaged endothelium in patients with preeclampsia with the associated platelet activation disturbs this balance, and it has been hypothesized that correcting this imbalance may prevent the progression of the disorder. The results of initial small studies using low-dose aspirin for its favorable effect on this balance were promising, but the recently published results of the multicenter Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) are disappointing.[53] In short, endothelial damage or dysfunction explains most if not all of the protean clinical manifestations of preeclampsia from the earliest detectable changes of increased pressor sensitivity to the most advanced changes, including renal failure, hepatic hemorrhage and rupture, seizure, and intracranial bleeding.

Diagnosis and Management of Patients With Preeclampsia

Diagnosis

In 1988 the Working Group on High Blood Pressure in Pregnancy was convened to develop a rigorous set of definitions to be used in the diagnosis of preeclampsia. According to its report published in 1990,[11] the definition requires the presence of hypertension along with either proteinuria or edema or both. The criterion of hypertension may be met by a rise of either 30 mm of mercury systolic or 15 mm of mercury diastolic over values measured before 20 weeks of gestation. If earlier values are unavailable, then any measurement taken after 20 weeks that is 140/90 mm of mercury or greater is considered hypertension. Proteinuria is defined as 0.3 grams (300 mg) or more of protein in a 24-hour urine collection. This is considered roughly equivalent to a dipstick reading of 1+ or greater. Edema is clinically evident swelling. The working group cautions that proteinuria is a relatively late-appearing sign and that edema may also present as fluid retention manifesting as rapid weight gain without evidence of swelling.

Having put forth the definition of preeclampsia given earlier, the working group acknowledges that many cases of preeclampsia will be missed if these guidelines are used too stringently. It emphasizes that preeclampsia is best overdiagnosed, and if it cannot be excluded, it is safest to manage the patient as though she had the disease.

Management

The goal of management in a patient with preeclampsia is to minimize end-organ damage and prevent progression to full-blown eclampsia while maximizing fetal viability ex utero. In some cases, this means immediate delivery, regardless of the risk of perinatal morbidity and mortality. In others, it can be considered safe to manage conservatively. In identifying indications for immediate delivery, it is important to make a distinction between mild and severe preeclampsia. Although, like the question of diagnosis, this question also calls for good clinical judgment, most of the agreed-on criteria are evidence of severe end-organ involvement or are associated with an unacceptably high risk of eclampsia or death. The criteria suggestive of severe preeclampsia are enumerated in the consensus report of the Working Group on High Blood Pressure in Pregnancy and include a blood pressure of 160/110 mm of mercury or higher, a urine protein concentration of greater than 2.0 grams (2,000 mg) in 24 hours, a serum creatinine level of greater than 110 μmol per liter (1.2 mg per dl) with previous values known to be normal, the presence of the HELLP syndrome or any component of it, headache or cerebral or visual disturbances, epigastric pain, and pulmonary edema.[11] A patient who meets any number of these criteria is classified as having severe preeclampsia and in many institutions would be treated with immediate delivery. In the past several years, however, increasing evidence suggests that many of these patients and their children can benefit from conservative management.[54,55] This idea is still controversial, and whereas some institutions have made conservative management of severe preeclampsia a policy, most others are reluctant to follow suit. In any case, that these patients require admission and immediate attention is not disputed. Aside from delivery, interventions currently practiced for severe preeclampsia are similar to those used in the mild form.

For a patient with mild preeclampsia in whom it is deemed safe to postpone delivery, various pharmacologic manipulations have been tried to minimize the risk of progression to severe preeclampsia or eclampsia. It is emphasized that these therapies are palliative only and, based on the understood pathophysiology of preeclampsia, cannot be curative. Until we understand more about the initiating processes in preeclampsia, the only diagnostic tools available measure abnormalities in maternal function, which occur after the placental lesion develops and takes its systemic toll. Therefore, in all of the preeclamptic patients we can identify, the damage has already been done.

The specific events generally targeted for prevention in the medical management of preeclampsia are cerebral hemorrhage and eclamptic seizures. Cerebral hemorrhage is thought to be caused by severe hypertension, and seizures are generally attributed to cerebral vasospasm. There is no evidence that controlling hypertension decreases the risk of eclamptic seizures. Nevertheless, antihypertensive drugs and medications aimed at seizure prophylaxis are the most common pharmacologic interventions used. Antiplatelet agents have also been tried in an attempt to avoid some aspects of the preeclamptic coagulopathy, particularly the HELLP syndrome.

Antihypertensive Agents

The Working Group on High Blood Pressure in Pregnancy recommends the use of antihypertensive medications only in patients with severe preeclampsia whose diastolic pressure reaches or exceeds 110 mm of mercury.[11] The major risk undertaken with the use of these drugs is the threat to the already tenuous uteroplacental circulation. Intravenous hydralazine hydrochloride has been the antihypertensive drug of choice in preeclampsia, but it has recently been removed from the market. Instead, clinicians are using nifedipine, labetalol hydrochloride, and methyldopa as primary alternatives.

The use of intravenous labetalol has been compared with that of hydralazine in several studies,[56-58] none of which showed a difference. It also seems not to be substantially different in reducing perinatal morbidity and mortality when compared with methyldopa.[59] Since the removal of hydralazine, then, individual institutions have adopted their own practices[60]; some favor the use of labetalol (M. L. Druzin, MD, Director of Maternal-Fetal Medicine, Stanford University Hospital, Palo Alto, California, written communication, April 1995), whereas others recommend the use of methyldopa.[11]

Still other clinicians routinely administer calcium channel blockers.[61] These have recently been shown to be safe alternatives to use during pregnancy.[62,63] The use of oral nifedipine, in a pregnant patient with chronic hypertension, has been shown to control blood pressure effectively without adversely affecting the results of Doppler waveform studies of uteroplacental blood flow.[64,65] Recent evidence suggests that nifedipine may be more effective than the standard hydralazine therapy in controlling the blood pressure and reducing perinatal complications.[66] Other studies have failed to show this, however.[67] An advantage of nifedipine use is that it is known to be an effective tocolytic, making it even more attractive in postponing delivery in a patient with preeclampsia remote from term. It should be noted that several investigators have found that the hypotensive effects of nifedipine are potentiated by the concurrent use of magnesium sulfate, a common antiseizure medication used in the management of preeclampsia.[68]

Anticonvulsive Drugs

Parenteral magnesium sulfate is the most widely accepted anticonvulsive drug for use in preeclampsia. Like nifedipine, it has attractive tocolytic activity and is,

in fact, used in tocolytic dosages for seizure prophylaxis. Its mechanism of action is not entirely understood. It was originally used as a calcium ion competitor to decrease smooth muscle reactivity and vasospasm, and indeed, the appropriate response to magnesium sulfate overdosing is to give parenteral calcium. There is some evidence, however, that magnesium sulfate infusion decreases the plasma levels of endothelin in preeclamptic women but not in those with normal pregnancies, suggesting a specific interaction between magnesium and the dysfunctional preeclamptic endothelium.[69]

Some clinicians have administered phenytoin for seizure prophylaxis,[70] but this intervention is somewhat controversial. Many clinicians doubt the soundness of the reasoning that justifies the use of a neuronal membrane stabilizer in a cerebrovascular disorder. In a small study, it was suggested that magnesium sulfate may even be more effective in eclamptic seizure prophylaxis.[71] Although antihypertensive drugs fail to treat the underlying process in the same way phenytoin does, their use is justified by the extensive end-organ damage attributable to uncontrolled hypertension. In addition, studies have shown the control of hypertension to be associated with improved perinatal outcome.[72]

Antiplatelet Agents

In an attempt to address the perceived role of disseminated intravascular coagulation in the pathogenesis of preeclampsia, antiplatelet agents have been tried. Primarily low-dose aspirin and occasionally dipyridamole have been used and found to confer no clear benefit in reducing the incidence of maternal and perinatal complications. In fact, some studies showed an increase in bleeding complications, particularly abruptio placentae.[73]

Another part of the rationale for the use of low-dose aspirin is that the prostacyclin-thromboxane imbalance is responsible for the general pressor sensitivity seen in patients with preeclampsia. Aspirin is an irreversible inhibitor of cyclooxygenase, a crucial enzyme in the production pathway of both eicosanoids. Because cellular turnover of cyclooxygenase is higher in endothelium than in non-nucleated platelets, it is predicted that, with low daily doses of aspirin, prostacyclin production by endothelial cells will recover more quickly than will platelet thromboxane production, thus restoring their balance. Indeed, several studies have measured the favorable effect of aspirin on the prostacyclin-thromboxane balance and associated it with decreased pressor sensitivity.[74,75]

The question of low-dose aspirin therapy in preeclampsia has been addressed by several studies. Two large trials recently published were the National Institutes of Health (NIH) trial in 1993[73] and the CLASP trial in 1994.[53] Both failed to show a clear benefit of low-dose aspirin therapy in routine preeclampsia prophylaxis, but both were able to identify subgroups in whom low-dose aspirin therapy reduced the incidence of preeclampsia. The NIH study of healthy primigravid women showed a benefit in women whose systolic blood pressure was 120 to 134 mm of mercury in the first half of their pregnancy. Although these authors found the incidence of abruptio placentae to be higher in the treated group compared with the group taking a placebo, they noted that the incidence was not elevated above that in the general population. The CLASP trial studied high-risk patients and found that, in the group with early-onset preeclampsia, low-dose aspirin therapy decreased the incidence of perinatal complications. It is not yet clear how best to identify that group in the general population.

Comments

Although much of the pathophysiology of preeclampsia appears explicable, the weakest links are those thought to be immune-mediated. These puzzles may not be solved until the immunology of pregnancy and preeclampsia is better understood. New therapies may yet be targeted to the eicosanoid balance, perhaps involving low-dose aspirin therapy in healthy primigravid women who meet the NIH criteria. Conservative management may become a more common practice in the future. In the interim, we can only optimize our current therapies to bring a patient with preeclampsia and her child to a delivery that is safe for both.

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REFERENCES

1. Chesley L: Hypertensive Disorders in Pregnancy. New York, NY, Appleton-Century-Crofts, 1978

2. Pritchard JA, Weisman R, Ratnoff OD, Vosburgh GJ: Intravascular hemolysis, thrombocytopenia and other hematological abnormalities associated with severe toxemia of pregnancy. N Engl J Med 1954; 250:89-98

3. Gaber LW, Spargo BH, Lindheimer MD: Renal pathology in preeclampsia. Bailliere's Clin Obstet Gynecol 1994; 8:443-467

4. Barron WM: The syndrome of preeclampsia. Gastroenterol Clin North Am 1992; 21:851-872

5. Lindoff C, Astedt B: Plasminogen activator of urokinase type and its inhibitor of placental type in hypertensive pregnancies and in intrauterine growth retardation: Possible markers of placental function. Am J Obstet Gynecol 1994; 171:60-64

6. Chesley L: Hypertensive Disorders in Pregnancy. New York, NY, Appleton-Century-Crofts, 1978

7. Zuspan FP: Chronic hypertension in pregnancy. Clin Obstet Gynecol 1984; 27:854-873

8. Turnbull AC: Maternal mortality and present trends, *In* Sharp F, Symonds EM (Eds): Hypertension in Pregnancy. Ithaca, NY, Perinatology Press, 1987, pp 135-150

9. Lindheimer MD, Katz AI: Preeclampsia: Pathophysiology, diagnosis and management. Annu Rev Med 1989; 40:233-250

10. Zuspan FP, Samuels P: Preventing preeclampsia (Editorial). N Engl J Med 1993; 329:1265-1266

11. Gifford RW, Chesley L, August P, et al: Consensus Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol 1990; 163:1689-1712

12. Friedman SA, Taylor RN, Roberts JM: Pathophysiology of preeclampsia. Clin Perinatol 1991; 18:661-682

13. Sheppard BL, Bonnar J: Ultrastructural abnormalities of placental villi in placentae from pregnancies complicated by intrauterine fetal growth retardation: Their relationship to decidual spiral arterial lesions. Placenta 1980; 1:145-156

14. Zuspan FP: New concepts in understanding of hypertensive disease during pregnancy: An overview. Clin Perinatol 1991; 18:653-659

15. Meekins JW, Pijnenborg R: A study of placental bed spiral arteries and trophoblastic invasion in normal and severely preeclamptic pregnancies. Br J Obstet Gynaecol 1994; 101:669-674

16. Zeek PB, Assali NS: Vascular changes in decidua associated with eclamptogenic toxemia. Am J Clin Pathol 1950; 20:1099-1109

17. Campbell DM, MacGillivray I, Carr-Hill R: Pre-eclampsia in second pregnancy. Br J Obstet Gynaecol 1985; 92:131-140

18. MacGillivray I: Some observations on the incidence of pre-eclampsia. J Obstet Gynaecol Br Comm 1958; 65:536-639

19. Feeney JG, Scott JS: Pre-eclampsia and changed paternity. Eur J Obstet Gynaecol Reprod Biol 1980; 11:35-38

20. Klonnoff-Cohen HS, Savitz DA, Cefalo RC, McCann MF: An epidemiologic study of contraception and pre-eclampsia. JAMA 1989; 262:3143-3147

21. Strickland DM, Guzick DS, Cox K, Gant NF, Rosenfeld CR: The relationship between abortion in the first pregnancy and development of pregnancy-induced hypertension in the subsequent pregnancy. Am J Obstet Gynecol 1986; 154:146-148

22. Seidman DS, Ever-Hadani P, Stevenson DK, Gale R: The effect of abortion on the incidence of pre-eclampsia. Eur J Obstet Gynecol Reprod Biol 1989; 33:109-114

23. Need JA: Pre-eclampsia in pregnancies by different fathers: Immunological studies. Br Med J 1975; 1:548-549

24. Feeney JG, Tovey LAD, Scott JS: Influence of previous blood-transfusion on incidence of pre-eclampsia. Lancet 1977; 1:874-875

25. Lichtig C, Deutsch M, Brandes J: Immunofluorescent studies of the endometrial arteries in the first trimester of pregnancy. Am J Clin Pathol 1985; 83:633-636

26. Labarrere CA, Althabe OH: Primary chronic abortion, preeclampsia, idiopathic intrauterine growth retardation, hydatidiform mole, and choriocarcinoma: A unifying concept. Am J Reprod Immunol Microbiol 1986; 10:156-157

27. Redman CWG: Immunological aspects of preeclampsia. Bailliere's Clin Obstet Gynecol 1992; 6:601-614

28. Park WW: Possible function of non-villous trophoblast. Eur J Obstet Gynaecol Reprod Biol 1975; 52:35-46

29. Unander AM, Olding LB: Habitual abortion: Parental sharing of HLA antigens, absence of maternal blocking antibody, and suppression of maternal lymphocytes. Am J Reprod Immunol 1983; 4:171-178

30. Beer AE, Quebbeman JF, Ayers JW, Haines RF: Major histocompatibility complex antigens, maternal and paternal immune responses, and chronic habitual abortions in humans. Am J Obstet Gynecol 1981; 141:987-999

31. Jenkins DM, Need JA, Scott JS, Morris H, Pepper M: Human leucocyte antigen and mixed lymphocyte reaction in severe pre-eclampsia. BMJ 1978; 1:542-544

32. Bolis PF, Martinetti Bianchi M, La Fianza A, Franchi M, Cuccia Belvedere M: Immunogenetic aspects of preeclampsia. Biol Res Pregnancy Perinatol 1987; 8:42-45

33. Fujisawa S: HLA antigens-antibodies system and its association with severe toxemia of pregnancy. Acta Obstet Gynecol Jpn [Nippon Sanka Fujinka Gakkai Zasshi] 1985; 37:124-130

34. Johnson N, Moodley J, Hammond MG: HLA-status in African women with preeclampsia. Br J Obstet Gynaecol 1988; 95:877-879

35. Kilpatrick DC, Gibson F, Livingston J, Liston WA: Pre-eclampsia is associated with HLA-DR4 sharing between mother and fetus. Tissue Antigens 1990; 35:178-181

36. Hoff C, Peevy K, Giattina K, Spinnato JA, Peterson RD: Maternal-fetal HLA-DR relationships and pregnancy-induced hypertension. Obstet Gynecol 1992; 80:1007-1012

37. Wilton AN, Barendse WJ, Donald JA: HLA-DRB types in pre-eclampsia and eclampsia. Tissue Antigens 1991; 38:137-141

38. Peterson RD, Tuck-Miller CM, Spinnato JA, Peevy K, Giattina K, Hoff C: An HLA-haplotype associated with preeclampsia and intrauterine growth retardation. Am J Reprod Immunol 1994; 31:177-179

39. Zeeman GG, Dekker GA, van Geijn HP, Kraayenbrink AA: Endothelial function in normal and pre-eclamptic pregnancy: A hypothesis. Eur J Obstet Gynecol Reprod Biol 1992; 43:113-122

40. Gryglewski RJ, Palmer RMJ, Moncada S: Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor. Nature 1986; 320:454-456

41. Dekker GA, Kraayenbrink AA, Zeeman GG, van Kamp GJ: Increased plasma levels of the novel vasoconstrictor peptide endothelin in severe pre-eclampsia. Eur J Obstet Gynecol Reprod Biol 1991; 40:215-220

42. Taylor RN, Varma M, Teng NN, Roberts JM: Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. J Clin Endocrinol Metab 1990; 71:1675-1677

43. Woodworth SH, Li X, Lei ZM, et al: Eicosanoid biosynthetic enzymes in placental and decidual tissue from preeclamptic pregnancies: Increased expression of thromboxane-A_2 synthase gene. J Clin Endocrinol Metab 1994; 78:1225-1231

44. Greenstein D, Henderson JM, Boyer TD: Liver hemorrhage: Recurrent episodes during pregnancy complicated by preeclampsia. Gastroenterology 1994; 106:1668-1671

45. Oosterhof H, Voorhoeve PG, Aarnoudse JG: Enhancement of hepatic artery resistance to blood flow in preeclampsia in presence or absence of HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets). Am J Obstet Gynecol 1994; 171:526-530

46. Greenspan FS, Baxter JD (Eds): Basic & Clinical Endocrinology, 4th edition. Norwalk, Conn, Appleton & Lange, 1994

47. Sealey JE, McCord D, Taufield PA, et al: Plasma prorenin in first trimester pregnancy: Relationship to changes in human chorionic gonadotrophin. Am J Obstet Gynecol 1985; 153:514-519

48. Gant NF, Daley GL, Chand S, et al: A study of angiotensin II pressor response throughout primigravid pregnancy. J Clin Invest 1973; 52:2682-2689

49. Schwarz R, Retzke U: Cardiovascular response to infusions of angiotensin II in pregnant women. Obstet Gynecol 1971; 38:714-718

50. Talledo OE, Chesley LC, Zuspan FP: Renin-angiotensin system in normal and toxemic pregnancies—3. Differential sensitivity to angiotensin II and norepinephrine in toxemia of pregnancy. Am J Obstet Gynecol 1968; 100:218-221

51. Roberts JM, Taylor RN, Goldfien A: Clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. Am J Hypertens 1991; 4:700-708

52. Chesley LC, Valenti C: The evaluation of tests to differentiate pre-eclampsia from hypertensive diseases. Am J Obstet Gynecol 1958; 75:1165

53. CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) Collaborative Group: CLASP: A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet 1994; 343: 619-629

54. Schiff E, Friedman SA, Sibai BM: Conservative management of severe preeclampsia remote from term. Obstet Gynecol 1994; 84:626-630

55. Schiff E, Friedman SA: Aggressive vs expectant management of severe pre-eclampsia at 28-32 weeks of gestation: A randomized, controlled trial. Am J Obstet Gynecol 1994; 171:812-822

56. Garden A, Davey DA, Dommisse J: Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. Clin Exp Hypertens 1982; 1:371-383

57. Mabie WC, Gonzales AR, Sibai BM, Amon E: A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy. Obstet Gynecol 1987; 70(pt 1):328-333

58. Walker JJ, Greer I, Calder AA: Treatment of acute pregnancy-related hypertension: Labetalol and hydralazine compared. Postgrad Med J 1983; 59(suppl):168-170

59. Redman CWG: A controlled trial of the treatment of hypertension in pregnancy with labetalol compared with methyldopa, *In* Riley AJ, Symonds EM (Eds): The Investigation of Labetalol in the Management of Hypertension in Pregnancy—International Congress Series 3591. Amsterdam, The Netherlands, Excerpta Medica, 1982, pp 101-110

60. Remuzzi G, Ruggenanti P: Prevention and treatment of pregnancy-associated hypertension: What have we learned in the last 10 years? Am J Kidney Dis 1991; 18:285-305

61. Connelly JF: Antihypertensive drugs of choice for the treatment of preeclampsia. Am J Hosp Pharm 1994; 51:1766-1767

62. Jannet D, Carbonne B, Sebban E, Milliez J: Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: A randomized comparative trial. Obstet Gynecol 1994; 84:354-359

63. Belfort M, Akovic K, Anthony J, Saade G, Kirshon B, Moise K Jr: The effect of acute volume expansion and vasodilation with verapamil on uterine and umbilical artery Doppler indices in severe preeclampsia. J Clin Ultrasound 1994; 22:317-325

64. Hanretty KP, Whittle MJ, Howie CA, Rubin PC: Effect of nifedipine on Doppler flow velocity waveforms in severe pre-eclampsia. Br Med J 1989; 299:1205-1206

65. Moretti MM, Fairlie FM, Akl S, Khoury AD, Sibai BM: The effect of nifedipine therapy on fetal and placental Doppler waveforms in preeclampsia remote from term. Am J Obstet Gynecol 1990; 163(pt 1):1844-1848

66. Fenakel K, Fenakel G, Appelman Z, Lurie S, Katz Z, Shoham Z: Nifedipine in the treatment of severe preeclampsia. Obstet Gynecol 1991; 77:331-337

67. Caruso A, Ferrazzani S: Use of nifedipine as first line therapy in gestational hypertension. Minerva Ginecol 1994; 46:279-284

68. Waisman GD, Mayorga LM, Cámera MI, Vignolo CA, Martinotti A: Magnesium plus nifedipine: Potentiation of hypotensive effect in preeclampsia? Am J Obstet Gynecol 1988; 159:308-309

69. Mastrogiannis DS, Kalter CS, O'Brien WF, Carlan SJ, Reece EA: Effect of magnesium sulfate on plasma endothelin-1 levels in normal and preeclamptic pregnancies. Am J Obstet Gynecol 1992; 167:1554-1559

70. Hutton JD, James DK, Stirrat GM, Douglas KA, Redman CW: Management of severe pre-eclampsia and eclampsia by UK consultants. Br J Obstet Gynaecol 1992; 99:554-556

71. Dommisse J: Phenytoin sodium and magnesium sulphate in the management of eclampsia. Br J Obstet Gynaecol 1990; 97:104-109

72. Ales KL, Norton ME, Druzin ML: The clinical significance of predictions based on screening second trimester mean arterial pressure: Adverse maternal [corrected] and infant outcomes. J Clin Epidemiol 1990; 43:117-124 [erratum published in J Clin Epidemiol 1990; 43:537]

73. Sibai BM, Caritis SN, Thom E: Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women—The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1993; 329:1213-1218

74. Wallenburg HCS, Dekker GA, Makowitz JW, Rotmans N: Effect of low-dose aspirin on vascular refractoriness in angiotensin-sensitive primigravid women. Am J Obstet Gynecol 1991; 164(pt 1):1169-1173

75. Sanchez-Ramos L, O'Sullivan MJ, Garrido-Calderon J: Effect of low-dose aspirin on angiotensin II pressor response in human pregnancy. Am J Obstet Gynecol 1987; 156:193-194

Conferences and Reviews

Cystic Fibrosis in Adults
From Researcher to Practitioner

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The Cystic Fibrosis Foundation currently tracks about 20,000 Americans with cystic fibrosis, an autosomal recessive genetic disease that leads to multisystem complications. With the institution of better therapeutic regimens over the past 2 decades, more patients with this disease are surviving to adulthood. Within the past decade, both clinical and basic science research in the field of cystic fibrosis has progressed at a rapid rate. The intent of this review is to introduce readers to the molecular, cellular, and systemic disorders of this disease. We discuss treatment strategies involving antibiotics, nutrition, immune-response mediators, chest physiotherapy, and sputum-active agents with respect to the airway dysfunction of cystic fibrosis. Other common complications, recent developments, transplantation, and gene therapy are also reviewed.

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Cystic fibrosis was first described in 1936 as a disorder separate from the "coeliac syndrome."[1] The term "cystic fibrosis of the pancreas" was coined two years later.[2] In 1964 a therapeutic plan for patients with cystic fibrosis was described that stressed the importance of airway clearance, nutrition, and the treatment of infection.[3] The principles of these therapeutic guidelines are still important to the caregivers of patients with cystic fibrosis, although methods have changed somewhat. The population of patients with cystic fibrosis has also changed; with better care, more patients are surviving to adulthood. As of December 1994, more than a third of the 19,517 patients in the United States registered with the Cystic Fibrosis Foundation (33.9%) were 18 years of age or older, the mean age had reached 15.3, and the mean survival of patients with cystic fibrosis in this country was 28.3 years. The oldest patient was 70 years old.[4] Cystic fibrosis is rapidly becoming a disease state of adults.

Within the past decade or so, research in this disease has progressed at an astonishing rate.* In 1989 the sequence of the cystic fibrosis gene was identified, with a 3-base-pair deletion resulting in the omission of a phenylalanine residue detected in patients with the disease. Only five years later, the initial trials of corrective gene transfer had involved more than 40 patients with cystic fibrosis, exceeding the total number of patients who have received gene therapy for all other genetic diseases combined.[5] Whereas some researchers see a cure on the horizon, many questions still need to be answered about the clinical efficacy and long-term safety of gene transfer. Nevertheless, the rapid progress of research has led to novel supportive therapies. In this review, we attempt to put into perspective the recent advances in the field.

*See also the editorial by D. C. Gruenert, PhD, "Cystic Fibrosis Therapy—Where We Are and How We Got There," on pages 361-362 of this issue.

Cystic Fibrosis Transmembrane Conductance Regulator

Because the protein product of the cystic fibrosis gene was unknown in 1985, investigators sought to find the gene by linkage analysis. The linkage relationship between paraoxinase and the cystic fibrosis gene was described,[6] and soon after a marker on chromosome 7 was discovered that was linked to both paraoxinase and the cystic fibrosis gene.[7] In 1989 a segment of DNA missing a codon for phenylalanine was identified and isolated from cystic fibrosis tissues but not from normal persons.[8-10] The gene product was designated the cystic fibrosis transmembrane conductance regulator, or CFTR. The *CFTR* gene is large, with 27 exons spanning 250 kilobases of genomic DNA at human chromosome 7q31.

Messenger RNA (mRNA) of *CFTR* has been identified in epithelia from lung (particularly in the airway submucosal glands),[11] sweat glands,[9] pancreas, intestinal crypts,[12] biliary ducts,[13] proximal and distal renal tubules, and the testes. This *CFTR* mRNA, which directs the synthesis of the 1,480-amino acid CFTR protein, is not abundant in lung epithelium as assessed by immunocytochemical methods.[12] More than 500 *CFTR* gene mutations that are associated with disease have been identified to date,[14] most of which are rare. The most common *CFTR* mutation, a deletion of the three bases coding for phenylalanine at position 508 ($\Delta F508$), accounts for almost 70% of mutant alleles.[15] An auto-

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ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
cAMP = cyclic adenosine monophosphate
CFTR = cystic fibrosis transmembrane conductance regulator
DNase = deoxyribonuclease
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
IV = intravenous
mRNA = messenger RNA
UTP = uridine triphosphate

somal recessive disease, cystic fibrosis affects 1 in 2,000 to 1 in 4,500 European whites and is the most common genetic disease in this group; the carrier rate is estimated to be 1 in 20. In populations of whites of non–northern European background and in nonwhites, the frequency of the *ΔF508* mutation in subjects with cystic fibrosis varies considerably.[16]

The *CFTR* gene contains 12 membrane-spanning domains, two nucleotide-binding regions, and a regulatory domain. It appears to couple adenosine triphosphate (ATP) hydrolysis with transmembrane chloride conductance across apical epithelial surfaces under cyclic adenosine monophosphate (cAMP)–dependent protein kinase A regulation.[17] The high frequency of cystic fibrosis carriers in whites of northern European background is speculated to be due to a selective advantage because of evidence that *CFTR* mutations convey resistance to bacterial toxin–mediated diarrheal disease. Intestinal chloride secretion in response to cholera toxin is diminished in *CFTR* (–/–) mice,[18] and rectal chloride secretion in response to *Escherichia coli* heat-stable enterotoxin is absent in patients with cystic fibrosis.[19] Besides being a chloride channel, CFTR likely has other physiologic functions, such as regulating other distinct ion channel proteins, that remain to be clarified.[20]

As shown in Figure 1, genetic mutations affecting transcription, translation, transport, and protein structure can all alter CFTR function.[21] Abnormal or absent CFTR function in respiratory tract epithelium can be demonstrated electrophysiologically by an increased negative (luminal side) transepithelial-potential difference.[22] This is explained by the fact that there is an abnormally accelerated rate of transepithelial sodium ion absorption in cystic fibrosis, supported by the fact that blocking sodium absorption with amiloride returns the respiratory tract transepithelial potential to normal.[23,24]

Under resting conditions in normal persons, sodium absorption drives water absorption from the airway lumen, and chloride accompanies sodium by a paracellular route. Chloride (and liquid) secretion presumably occurs by cAMP-regulated CFTR channels. In cystic fibrosis, then, the excessive sodium absorption and the absent chloride secretion through CFTR channels leads to the dehydration of airway surface fluids.[23,24]

The cAMP-stimulated sodium-absorptive channels responsible for this increased sodium permeability appear to be regulated by CFTR through an as-yet-incompletely understood mechanism.[25,26] The CFTR product is also functionally linked to other chloride channels designated as outwardly rectifying chloride channels through CFTR-dependent and cAMP-stimulated ATP release.[27] Thus, the actual chloride secretion through CFTR channels may represent only a portion of a much larger spectrum of CFTR-regulated ion transport processes.

Specific *CFTR* genotypes do not correlate well with disease severity. For example, patients homozygous for the *ΔF508* mutation will almost always have pancreatic insufficiency and abnormal sweat chloride values, but their pulmonary disease varies from mild to severe, even in the same family.[28] The genetic elements responsible for the regulation of *CFTR* expression within a defined genotype remain largely undefined. Mislocalization of the mutant CFTR protein to an abnormal cellular position also contributes to differences in phenotype expression. The CFTR protein can be identified in apical regions of normal airway epithelial cells and in cytoplasmic regions of cells from cystic fibrosis subjects.[29] A *ΔF508-CFTR* gene leads to the production of a CFTR protein that is incompletely processed (see Figure 1). Because of its intracellular location, ΔF508-CFTR is essentially nonfunctional.

Other *CFTR* mutations result in normal localization of the protein product to the apical surface of the cell membrane, but the chloride channel is dysfunctional. An example is the missense mutation R117H in the first transmembrane domain. This *CFTR* mutation produces

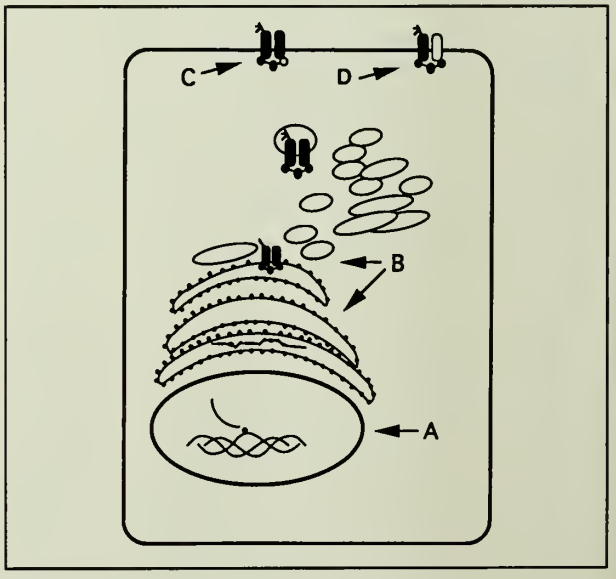

Figure 1.—The mechanisms of *CFTR* gene mutations are shown. Class I mutations are due to defects in protein production resulting in unstable messenger RNA or aberrant protein (**A**). Class II mutations lead to defective protein processing and result in mislocalization of CFTR or degradation of the abnormally located protein (**B**). Class III mutations cause abnormalities in nucleotide-binding domains, and *CFTR* genes with these mutations have varying amounts of activity (**C**). Class IV mutations lead to abnormalities of membrane-spanning domains and variable effects on the chloride ion current (**D**) (adapted from Welsh and Smith[21]).

a CFTR channel with about 15% of normal apical membrane chloride conductance[21] and is among the 5% to 10% of *CFTR* mutations that confer a pancreatic-sufficient phenotype.[30]

Although it seems that mutations producing a partly functional CFTR should lead to an attenuated phenotype, the effect of an abnormal *CFTR* varies, as observed in some patients with *ΔF508/ΔF508* genotypes and mild lung disease. It may also be difficult to predict the phenotype of compound heterozygote patients who possess two different *CFTR* mutations. It is thus apparent that *CFTR* mutations alone cannot fully explain the variable local disease within persons and that other genetic and nongenetic factors contribute to the broad range of clinical severities seen in fibrocystic lung disease.

Airway Sepsis and Inflammatory-Immune Processes

The hallmark tenacious sputum of persons with cystic fibrosis transforms normal airway mucociliary defense and transport systems into a hospitable environment for bacterial pathogens. It has recently been speculated that the undersialylated apical membrane of fibrocystic epithelia may contribute to the pathogenesis of airway infection in patients with this disease.[31] Initially *Staphylococcus aureus* infects a patient's lungs, and the resulting airway inflammatory-immune processes eventually damage respiratory tract epithelial surfaces. This damage predisposes the airways to infection with *Pseudomonas aeruginosa*,[32] which may be identified in cystic fibrosis patients as young as 3 years. Chronic infection with *P aeruginosa* is established around age 8,[33] and ineffective but tissue-damaging inflammatory-immune responses eventually compromise respiratory tract mucociliary clearance. Inflammatory mediators act on CFTR chloride channels in normal airways to cause an increase in submucosal gland fluid secretion and a decrease in net fluid absorption across the surface epithelium. Fibrocystic sputum supernatant, in fact, is a potent inducer of secretion from serous cells of normal airway glands.[34] In inflamed airways of patients with this disease, without the contribution of CFTR, decreased gland fluid secretion and increased fluid absorption by the surface epithelium serve to dehydrate the airway mucus.[35] Impaired mucociliary clearance may be demonstrated even in patients with normal small airways function.[36] Further deterioration may develop in persons with mutations expressed as partially functional CFTRs because *CFTR* expression is decreased in remodeled respiratory epithelium such as that found in patients with chronic airway infection.[37]

Pseudomonas aeruginosa produces a broad spectrum of ciliotoxins, proteases, and exotoxins.[38-40] In vitro, *P aeruginosa* demonstrates chemotaxis toward and adheres to respiratory mucins.[41] In most cases of infection, a single strain of *P aeruginosa* infects a patient and, over time, expresses a critically important alginate gene, resulting in transformation to a mucoid form.[42] This transformation to a mucoid form is promoted by environmental conditions. Mucoid transformation can be observed in *P aeruginosa* grown in suboptimal nutritional media[43] and in hyperosmolar media,[44] conditions probably present in the airways of patients with cystic fibrosis.

In cystic fibrosis airways, the *P aeruginosa* alginate combines with calcium ion to form a fibrous anionic matrix that envelops microcolonies of organisms[45] and compromises the defensive phagocytic mechanisms of the host. The alginate gel may directly antagonize β-lactam and aminoglycoside antibiotics and physically prevent antibiotics from acting on the *P aeruginosa* microcolonies.[42]

Because of the thick, tenacious mucus, airway infection persists and is accompanied by a sustained host inflammatory-immune response. Alveolar macrophages present antigen to activate T-helper lymphocytes, which express cytokines such as interleukins-2, -3, -4, -5, -6, and -8. In response to particular cytokines, T-helper lymphocytes proliferate, B lymphocytes are transformed to plasma cells that generate antibodies, and granulocytes are attracted and activated.[32] Stimulated neutrophils release large amounts of oxidants and proteases, including elastase.[46] The "free" elastase is thought to play an important role in both the mucous oversecretion[34] and the progressive lung destruction seen in cystic fibrosis patients. Sputum from patients with mild cystic fibrosis pulmonary disease (mean forced expiratory volume in 1 second [FEV_1], 95% of predicted) contains a substantially increased amount of neutrophils and immunoglobulins and abundant active elastase.[47] An elastase-antiprotease imbalance is established in the airways of some patients as young as 1 year.[48]

As with *Staphylococcus* and *Pseudomonas* species, nontuberculous mycobacteria may cause clinical disease in patients with cystic fibrosis. About 20% of such patients screened for nontuberculous mycobacteria have been sputum culture–positive.[49] Difficulties can arise in recognizing the pathogenic presence of nontuberculous mycobacteria in patients with chronic fibrocystic lung disease, given that primary atypical mycobacterial infections may also lead to bronchiectasis. Many patients with cystic fibrosis with cultures positive for these organisms do not require treatment.

Berkholderia (formerly *Pseudomonas*) *cepacia* is a multidrug-resistant gram-negative bacterium found in chronically infected patients with cystic fibrosis and is associated with severe lung disease and increased morbidity and mortality. Ribotyping has suggested that *B cepacia* can be transmitted by person-to-person contact (for example, cystic fibrosis summer camps).[50] A more recent study using more discriminative techniques, however, demonstrated a lack of transmission among patients followed at a cystic fibrosis center, thus suggesting variable transmissibility among strains of *B cepacia*.[51]

Antibiotic Strategies

Antibiotics remain the cornerstone of the treatment of airway sepsis, and the use of effective antipseudomonal antibiotic strategies has contributed to the improved survival of patients with cystic fibrosis. For moderate to severe exacerbations of pseudomonal air-

way sepsis, parenteral aminoglycoside courses of two to three weeks are conventionally administered in combination with another antipseudomonal drug. Parenteral aminoglycosides are perhaps the best-studied antibiotic agents in these patients, yet their volume of distribution and total body clearance rates remain incompletely characterized. Current aminoglycoside prescribing practice is to administer tobramycin at 9 mg per kg of body weight per day intravenously (IV) in three divided doses.[52] Pilot studies have been done of less frequent parenteral aminoglycoside dosing (such as every 12 hours) in cystic fibrosis patients, and the results appear promising.[53,54] Aminoglycosides accumulate in fibrocystic sputum over time, and with constant dosing, sputum levels may continue to increase over weeks.[55] Prolonged hospital stays are usually not necessary, provided stable IV access—for example, peripherally inserted central venous catheters or permanent central venous access ports—and a comprehensive home care system are available. The financial benefit of home care is substantial. With appropriate support, consisting of home nursing and drug and efficient respiratory therapy strategies, the risks are few.[56]

Antipseudomonal penicillins and cephalosporins also show an increased volume of distribution and total body clearance in patients with cystic fibrosis. An increased frequency of sensitivity reactions to piperacillin has been observed.[57] Ceftazidime is generally favored by clinicians over piperacillin or ticarcillin for the outpatient treatment of *P aeruginosa* because of its less frequent dosing requirement.

Other antipseudomonal drugs include aztreonam, the combination of imipenem and cilastatin sodium, and ciprofloxacin. Aztreonam is a synthetic molecule with little allergenic potential, and it can be used in patients sensitive to β-lactam antibiotics. Its acyl side chain, which confers its antipseudomonal activity, is similar to that of ceftazidime. Organisms resistant to ceftazidime may then also be resistant to aztreonam. Ciprofloxacin is a potent antipseudomonal antibiotic that inhibits DNA gyrase; resistance to this drug may develop rapidly during monotherapy. It represents a useful drug to reserve for intermittent oral outpatient use, often in combination with aerosolized aminoglycosides.

Much interest has been generated in the aerosolization of antibiotics, particularly aminoglycosides. Aerosolization allows the direct delivery of high drug concentrations to the site of infection without risk of nephrotoxicity or ototoxicity and permits patients to initiate or continue effective antibiotic therapy as outpatients. A recent 71-patient multicenter, double-blind, placebo-controlled crossover study demonstrated the effectiveness of a 600-mg, three-times-a-day regimen of ultrasonically nebulized tobramycin in increasing FEV_1 and forced vital capacity (FVC) in patients with cystic fibrosis. Sputum density of *P aeruginosa* in the treatment group decreased by a factor of 100. The frequency of the emergence of tobramycin-resistant *P aeruginosa* was not increased.[58] These high doses of tobramycin are relatively expensive, but less so than administering IV antibiotics. Other investigators have found lower doses effective.[59,60] At present, sterile tobramycin (packaged for parenteral use) can be dispensed in 80-mg vials. An often-used regimen is 80 to 160 mg of tobramycin administered twice a day with a bronchodilator through a high-quality (3- to 5-μm particle) nebulizer. Clinical progress is monitored, and the tobramycin dosage is adjusted if necessary. The efficacy of a concentrated, commercially prepared tobramycin solution for inhalation is currently being studied.

Inflammatory-Immune Response Strategies

The exuberant inflammatory-immune response to continuing airway sepsis is regarded as a major pathogenic mechanism of pulmonary damage in cystic fibrosis. Because eradicating airway bacterial pathogens is impossible, the control of the inflammatory response becomes an important therapeutic consideration.[61] Increasing attention is being directed toward the role of neutrophils and cytokines as important mediators of tissue destruction in cystic fibrosis and other inflammatory diseases. Strategies designed to reduce the putative deleterious effects of neutrophils without inhibiting the beneficial actions of these cells are being actively explored.

Administering prednisone (2 mg per kg) on alternate days was initially found to improve growth and pulmonary function in children with mild to moderate lung disease without causing steroid-related complications.[62] This study was repeated on a larger scale in 6- to 14-year-olds with cystic fibrosis using both 2-mg-per-kg and 1-mg-per-kg alternate-day prednisone dosing, and it was found that linear patient growth was substantially reduced with both regimens. Noninfected patients taking steroids became infected with *P aeruginosa* at a faster rate than noninfected patients taking placebo. Infected patients in the steroid group had improved FEV_1 and FVC for 24 months compared with those in the placebo group, but hospitalization rates were similar.[63] Given these results, there may be a role for alternate-day corticosteroid use in adults, although controlled studies have yet to be done.

Ibuprofen inhibits several aspects of neutrophil function, and its use was found to decrease inflammation in a rat model of chronic *P aeruginosa* infection without increasing the lung bacterial burden. Low plasma concentrations of ibuprofen, however, increase lung inflammation in animal models. In a recent four-year trial, a group of cystic fibrosis patients with mild lung disease (mean FEV_1 of 87.5% ± 1.8% [standard deviation] of predicted) received 20 to 30 mg per kg of ibuprofen twice a day versus placebo. Pharmacokinetics were used to assure peak plasma ibuprofen concentrations of 50 to 100 μg per ml. Among subjects completing the study, the annual rate of decline in the percentage of predicted FEV_1 and FVC was decreased by 59% and 57%, respectively, relative to the use of placebo, without an increase in gastrointestinal complications.[64] The study demonstrated the effectiveness of carefully monitored high-dose ibuprofen therapy in persons with mild fibrocystic

lung disease. Studies of dose-response relationships in patients with more severe fibrocystic lung disease are needed, however.

Pentoxifylline may be effective in decreasing neutrophil-induced injury in fibrocystic lungs, perhaps by inhibiting the production of tumor necrosis factor α, which "primes" neutrophil responses to subsequent stimuli. A small pilot study has demonstrated pentoxifylline's usefulness in maintaining the baseline sputum neutrophil-elastase concentration and improving the FVC. Administering pentoxifylline also reduced the number of serious pulmonary exacerbations.[65] A larger study is needed.

Further investigations are required to determine if modulators of fibrocystic airway inflammatory-immune processes are efficacious and safe in patients with more severe lung disease. Controlled studies of blocking or neutralizing neutrophil products involved in the inflammatory response and subsequent tissue destruction need to be considered. Preliminary data suggest that lung injury resulting from the instillation of fibrocystic sputum sol into rat lungs is prevented when the rats are pretreated with an oral neutrophil-elastase inhibitor.[66] Clinical investigative efforts should take into account the current degree of inflammation within the fibrocystic airways studied. As such, this endeavor will require the use of assays to demonstrate changes in protease, antiprotease, oxidant, antioxidant, and cytokine concentrations that should be correlated to clinical state.

Vaccines against *P aeruginosa* antigens are actively being investigated. Paradoxically, a positive correlation between high levels of anti–*P aeruginosa* antibody titers and a more severe disease course has been observed. Although anti–*P aeruginosa* lipopolysaccharide antibodies acquired after infection have poor opsonic activity, opsonic vaccine-induced antibodies may be useful to prevent or delay airway infection with *P aeruginosa*. A small recent study has demonstrated the safety of a polyvalent *P aeruginosa* vaccine in noninfected patients with cystic fibrosis (mean age of 8 years). Although results suggested the need for frequent booster vaccinations, 19 of 30 patients studied remained free of *P aeruginosa* isolates for three years.[67]

Malabsorption or Nutrition

Defective *CFTR* in the pancreatic duct epithelium usually leads to increased viscosity of pancreatic secretions; the blockage of pancreatic ducts; pancreatitis (usually "silent"); and the end results of carbohydrate, protein, and especially fat malabsorption. Endocrine pancreatic insufficiency develops in only a minority of patients. High-fat diets with supplemental pancreatic enzymes are advocated.[68] Nearly 94% of all the patients in the cystic fibrosis registry take pancreatic enzyme supplements, and 5% require insulin.[4] Supplemental doses of 500 to 1,500 units per kg of lipase per meal and less for snacks are usual. Stool frequency and stool flotation are clinically useful measurements to guide enzyme dosage, although quantitative studies of fecal fat are more definitive. Microencapsulated pancreatic formulations are designed to dissolve in the distal duodenum. The various formulations have differing dissolution profiles and amount of enzyme "overfill."[69] Because enteric-coated formulations require a pH of about 5.6 to 6.0 for dissolution, some patients with severely reduced pancreatic bicarbonate secretion may have poor fat absorption despite high enzyme dosages. The administration of histamine-H_2 antagonists or omeprazole should be considered for patients requiring more than 2,000 units per kg of lipase for meals.

Colonic strictures have been reported in patients with cystic fibrosis receiving high-dose pancreatic enzyme replacement (>40,000 units of lipase per kg per day).[70] Abdominal ultrasonography has been used to detect colonic thickening and has shown a significant correlation between the mean daily units of protease per kg of body weight and the maximum thickness of the ascending colon.[71]

Patients can become unable to meet their increased caloric needs when airway sepsis becomes severe or the work of breathing becomes increased, particularly in the later stages of the disease. Other factors contributing to malnutrition include anorexia, depression, and fatigue. The distal intestinal obstruction syndrome, a form of acute or subacute bowel obstruction similar to a meconium ileus, can cause postprandial discomfort and lead to anorexia and weight loss. The interrelations between nutritional state, airway sepsis, further decrements in lung function, and survival are well recognized.[72]

Many oral nutritional supplements are commercially available. If patients cannot maintain adequate weight (at least 80% of ideal body weight), supplemental tube feedings may be used. There are no controlled trials of nutritional support by this route, but tube feeding, usually by gastrostomy, allows patients to take in 25% to 30% of their daily caloric requirements while sleeping. Patients considered for gastrostomy tube placement generally have severe pulmonary disease and require a program of augmented chest physiotherapy and antibiotics to prepare them for the procedure.

Patients with pancreatic insufficiency are at risk for deficiencies in fat-soluble vitamins. Overt symptoms of vitamin A deficiency are rarely encountered, although biochemical evidence of deficiency can be observed. Likewise, vitamin E deficiency does not usually manifest as clinical disease except in cases of long-standing deficiency. Osteopenia and kyphosis are well recognized in cystic fibrosis patients and are likely multifactorial, but vitamin D deficiency is a concern in patients with inadequate exposure to sunlight or with cholestatic liver disease. Vitamin K deficiency may manifest as coagulation abnormalities in adults with cystic fibrosis with cholestatic liver disease or on long-term parenteral antibiotic therapy. Supplemental vitamin K, 5 mg two to three times a week, is prophylactically prescribed for these patients. Supplemental vitamin E, 200 to 400 IU per day, is recommended, although data on the benefits to patients are lacking. Yearly measurements of serum

retinol (vitamin A) and tocopherol (vitamin E) levels are recommended.[73]

Other nutritional supplements have been advocated for use by cystic fibrosis patients to provide either anti-inflammatory or antioxidant effects. Plasma carotenoid levels are known to be low in most children with cystic fibrosis.[74] Increased lipid peroxidation occurring in β-carotene–deficient patients has been claimed to be normalized by supplementation.[75] Dietary supplements containing ω3 fatty acids may have an anti-inflammatory effect[76] and may decrease the neutrophil release of leukotriene B_4, an important neutrophil chemoattractant that is increased in bronchoalveolar lavage fluid of cystic fibrosis patients.[77] A recent study showed that the oral absorption of ω3 fatty acids in pancreatic insufficient cystic fibrosis patients is approximately half that of healthy controls.[78] Unfortunately, clinically beneficial effects with the use of antioxidant or anti-inflammatory nutritional supplements have not been reported, and no specific recommendations can be made at this time.

Hepatic and Biliary Tract Disease

The *CFTR* gene is abundant in intrahepatic biliary epithelial cells and plays a role in biliary secretion. In cystic fibrosis, the biliary tract secretions become more viscous and can lead to stasis with resultant biliary cirrhosis. A relative increase in the bile acid pool's hepatotoxic hydrophobic fraction may contribute to this process. Pathologic changes suggest a progression of disease from cholestasis through focal periportal fibrosis to, in some severely affected patients, multilobular biliary cirrhosis and portal hypertension. The contribution of common bile duct strictures to the development of liver disease is controversial. Endoscopic retrograde cholangiography did not confirm the striking association between bile duct abnormalities and liver disease observed in an earlier study using percutaneous cholangiography to examine the biliary tree.[79]

Recent studies have shown that clinical, biochemical, and ultrasonographic evidence of liver disease is fairly common in cystic fibrosis. Liver disease is noted in about 20% of patients with cystic fibrosis and is often associated with a history of meconium ileus or its adult equivalent, the distal intestinal obstruction syndrome. Liver disease is almost always associated with pancreatic insufficiency,[80] although it has been reported in a few patients who have pancreatic sufficiency and common bile duct abnormalities.[81] The average age of the onset of liver disease in patients with cystic fibrosis, as suggested by a persistent elevation in liver enzyme levels, is 7 years (range, 5 to 17 years).[82] A progression to more severe liver involvement is rare; only 0.9% of the patients registered with the Cystic Fibrosis Foundation are reported to have cirrhosis with portal hypertension.[4] Screening for liver disease should consist of a history, physical examination, and biochemical testing. Ultrasonography is confirmatory and can be used to show portal hypertension, if present.

As in primary biliary cirrhosis, ursodeoxycholic acid because of its choleretic properties may be beneficial for cystic fibrosis patients with liver disease.[83] The ability of ursodeoxycholic acid to stabilize liver function in these patients is currently the subject of a multicenter trial.

Symptomatic gallbladder disease is a known complication of cystic fibrosis in adults. Cholelithiasis or a shrunken gallbladder may be observed on ultrasonography or scintigraphy. Although the cause of microgallbladder is unknown, cholelithiasis is likely a result of the decreased total bile acid pool and a relative overabundance of cholesterol, which is normally solubilized by bile salts.[84] There may also be some contribution by inspissated secretions acting as niduses for stone formation. Laparoscopic cholecystectomy may be a useful option because it should lead to less postoperative splinting of respiration.

A recent retrospective survey showed that although the overall occurrence of cancer in cystic fibrosis patients was within the expected range, the incidence of cancer involving all parts of the gastrointestinal tract was increased 6.5-fold over expected numbers.[85]

Airway Clearance

The use of techniques to augment airway clearance slows the progression of obstructive pulmonary disease in cystic fibrosis.[86] Compliance with conventional postural drainage and percussion in adults is, however, notoriously low.[87] As patients reach their teens, greater compliance may be obtained through the advocacy of airway clearance techniques that do not require assistance or a lengthy time commitment.

Autogenic drainage is an independent method of airway clearance that primarily involves using controlled breathing techniques. It requires extended instruction and a considerable time commitment (30 to 45 minutes per session). Although attractive because it does not require additional devices, busy patients will likely opt for another method. The active cycle of breathing technique, consisting of sequences of active chest expansion exercises and forced expirations, requires less time commitment but is probably as effective.[88]

Positive expiratory pressure treatment, another airway clearance method, is an effective and convenient option for adults with cystic fibrosis. It is performed with either a face mask or a mouthpiece attached to a one-way valve with a set resistance of 5 to 20 cm of water. A positive expiratory pressure treatment requires two minutes; safe performance of this technique requires educating patients.[89]

The Flutter (Vario-Raw S.A., Aubonne, Switzerland) is another airway clearance device that is popular with adults with cystic fibrosis. Approved by the US Food and Drug Administration for use in 1994, this small, sturdy device is handheld and resembles a covered pipe. The bowl of the pipe contains a steel ball that, during expiration, produces oscillations of variable expiratory resistance. Use of the Flutter has been shown to be more

effective, in terms of weight of sputum produced, than voluntary cough or percussion with postural drainage.[90]

High-frequency chest compression using an inflatable vest driven by a pulsed-air delivery system represents another option.[91] The vest can be worn while seated so that other tasks may be performed. The action of the vest is distracting, however. Oral high-frequency oscillation units represent a second use for the high-frequency oscillation ventilator technology. These units are analogous to high-frequency chest compression and may increase mucociliary clearance.[92] Both devices are costly, but may be useful adjuncts to other forms of physiotherapy, especially in hospitalized patients.

Although a formal exercise program is probably useful in assisting airway clearance and maintaining FEV_1 values,[93] it is important to recognize the necessity for patients with cystic fibrosis to practice another technique of physiotherapy as a primary modality for clearing the airways. As may be suspected, it is difficult to compare the efficacies of the various modes of chest physiotherapy for adults with the disease. Disease severity, social and psychological situations, and trials of several physiotherapy methods are often taken into consideration before decisions are made concerning the most appropriate airway clearance technique for a given patient.

Sputum-Active Agents

A large number of neutrophils are present and their constituents highly active in the thick, tenacious sputum of cystic fibrosis patients. The DNA derived largely from degenerating neutrophils is present at concentrations approaching 6 mg per ml,[94] which contributes to the viscoelastic properties of the sputum. Bovine deoxyribonuclease (DNase) I had been used as a mucolytic agent based on in vitro data indicating that the cleavage of DNA-laden sputum would decrease viscosity. The bovine DNase preparations, however, contained contaminants that were bronchial irritants. More recently, recombinant human DNase I has been effective in vitro at reducing fibrocystic sputum viscosity.[95]

A recent randomized, double-blind, placebo-controlled, 24-week study of 968 patients with cystic fibrosis was performed comparing the use of 2.5 mg of aerosolized recombinant human DNase once a day and twice a day with that of placebo. Administering recombinant human DNase once and twice a day improved FEV_1 values an average of 5.8% ± 0.7% and 5.6% ± 0.7% from baseline, respectively. Voice alteration was the most common adverse event in treated patients (14%). Administering recombinant human DNase once a day led to small reductions in the number of days patients required parenteral antibiotic therapy (11.2 to 8.5 days) and in the duration of hospital stays (6.9 to 5.6 days).[96] Patients in the treatment groups of the phase III trial who continued on DNase therapy have shown a continued trend toward less airway sepsis.[97] Based on the factory cost of recombinant human DNase of $27 for a 2.5-mg dose, this slight reduction in the number of parenteral antibiotic and hospital days came at a pharmacy cost of $4,536.[96] The selection of patients for recombinant human DNase therapy includes those with reductions in FEV_1 or FVC (<70% of predicted), those who comply with chest physiotherapy, those frequently admitted to a hospital or on parenteral antibiotic therapy, and arguably those who have shown an improvement in their FEV_1 after a four-week trial of recombinant human DNase.

Like DNA, actin, which comprises 10% of total leukocyte protein, is abundant in fibrocystic sputum and contributes to its high viscosity. Gelsolin is a native human protein that breaks noncovalent bonds between actin filaments. Gelsolin diminishes the viscosity of fibrocystic sputum specimens more efficiently and rapidly than bovine pancreatic DNase I and appears to act synergistically with DNase I on sputum. Gelsolin holds great promise as a mucolytic for patients with this disease.[98]

Amiloride is a diuretic that, when aerosolized, acts as a sodium channel blocker and inhibits the overexuberant sodium transport from the airway lumen in cystic fibrosis patients. Aerosolized uridine triphosphate (UTP), in the presence of amiloride, activates non-CFTR chloride channels and stimulates the secretion of chloride and water into the airway lumen. Extracellular nucleotides such as UTP also cause goblet cell degranulation and an increase in ciliary beat frequency. Combination therapy appears to be safe and improves mucociliary clearance in adult patients.[99] Further clinical trials of amiloride and UTP are needed to evaluate the long-term efficacy of these approaches, and some are currently underway.

N-Acetylcysteine has been advocated as a mucolytic, but its long-term usefulness in patients with cystic fibrosis remains unproved. Small European trials have failed to demonstrate substantial improvements in the peak expiratory flow rate, FEV_1, FVC, ciliary motility, or ciliary beat frequency in cystic fibrosis patients receiving oral *N*-acetylcysteine.[100,101] Nebulized or intratracheally instilled *N*-acetylcysteine may cause irritation and bronchospasm. The use of oral *N*-acetylcysteine for pulmonary mucolysis in patients with cystic fibrosis is not recommended.

Other Complications of Cystic Fibrosis

Pneumothorax is a complication in patients older than 18 with cystic fibrosis and usually suggests the presence of severe lung disease. About 20% of these patients will acquire a pneumothorax during their lifetime. Small, asymptomatic pneumothoraces may be managed conservatively with inpatient observation; large or symptomatic pneumothoraces require chest tube thoracostomy.[102] Because the complication rate increases with successive days of chest tube drainage, after five days of unsuccessful treatment, other measures need to be considered. For most patients with a progressive loss of pulmonary function, future candidacy for lung transplantation is a concern, and effective chemical pleurodesis for pneumothoraces renders a prospective pneumonectomy more difficult. It might be more appropriate initially to attempt corrective thoracoscopic measures such as oversewing, laser ablation, stapling, and directed pleurodesis.

Chemical pleurodesis is a more appropriate consideration for patients who are not transplantation candidates or who are poor candidates for even thoracoscopic procedures.

Bloody streaking of the sputum is common in patients with cystic fibrosis and may accompany exacerbations of airway sepsis. It does not require specific treatment. Major hemoptysis, defined by the Cystic Fibrosis Foundation as more than 240 ml per day or requiring transfusion, occurs in 1% of affected patients per year,[4] with most patients being older than 16 years. Major hemoptysis is nearly always of systemic arterial origin. A careful examination is indicated to rule out other possible sources and causes of hemorrhage—including drugs and coagulation defects—and to localize the bleeding. Bronchoscopy may be helpful if the bleeding is persistent; IV conjugated estrogen (Premarin), IV vasopressin, endobronchial tamponade or topical therapy, and bronchial artery embolization may be useful to achieve hemostasis.[102]

In a recent review of 236 patients, 25% were found to have colonies of *Aspergillus fumigatus* on sputum culture. Of those colonized, 25% had peripheral eosinophilia, immediate cutaneous reactivity to *A fumigatus*, and elevated serum immunoglobulin E levels.[103] Clinical signs of allergic bronchopulmonary aspergillosis may be difficult to differentiate from cystic fibrosis because not all features of allergic bronchopulmonary aspergillosis may be present at once, nor are all specific. Serologic tests may not even be helpful in diagnosing this disorder because variable immune responses to *A fumigatus* have been observed in cystic fibrosis patients. Patients also have had diminished immune responsiveness and clinical improvement over time with supportive therapy alone.[104] Corticosteroids remain the treatment of choice for allergic bronchopulmonary aspergillosis. Ketoconazole has been used successfully in a few patients with the disease who are poorly responsive to corticosteroids,[105] but it can be recommended only for patients with noninvasive disease.

The presence of *CFTR* in the paranasal sinus epithelial cells modifies the composition and viscoelastic properties of nasal mucus. The abnormal nasal mucus in cystic fibrosis leads to mechanical obstruction of the sinus ostia, local hypoxia and hypercarbia, mucosal edema, and ciliary injury.[106] Sinus infection and the resultant inflammation will worsen the obstruction of sinus ostia. Sinus disease develops in most patients with cystic fibrosis at some point in their lifetime, with nasal polyposis developing in 10% to 32%.[107] An unusual complication of polyposis is the development of mucoceles, most commonly in the frontal sinuses. These mucoceles may lead to strabismus, diplopia, blurred vision, and bony erosion. Computed tomographic scanning is necessary to evaluate for the presence of bony erosions and to plan for operative intervention.[108] The medical management of polyposis and sinus disease consists of a long (3 to 6 weeks) course of oral antibiotics and topical corticosteroid nasal spray. No formal studies have been done to demonstrate the effectiveness of corticosteroid nasal sprays in cystic fibrosis. A response to medical therapy—intranasal and oral corticosteroids with antihistamines—with a complete disappearance of polyps has been reported, with rates as high as 31%.[109]

Indications for the surgical management of sinus disease in patients with cystic fibrosis include chronic nasal obstruction with mouth breathing, chronic purulent nasal discharge unresponsive to medical treatment, and persistent headaches thought to be due to sinusitis.[107] Polyp recurrence is common following simple polypectomies. When polypectomies are done in conjunction with paranasal sinus surgical treatment, the recurrence rate can be as low as 13%.[110] Because the underlying disease responsible for the development of sinusitis is not corrected, aggressive postoperative management to reduce inflammation, such as sinus irrigation and topical corticosteroid nasal spray, is recommended.

Rheumatologic syndromes, an infrequent complication of cystic fibrosis, are recognized in 2.5% to 12% of patients. The more common episodic form of arthropathy is generally a symmetric polyarthropathy with a sudden onset that lasts five to seven days. The age of onset is from 13 to 20 years, and patients do not differ with regard to pulmonary function, respiratory pathogens, gastrointestinal disease, or treatment. The other major rheumatologic complication is hypertrophic pulmonary osteoarthropathy, with a median age of onset of 20 years. In most cases, it is symmetric and may be accompanied by joint effusions. This disorder is recognized in patients with more severe lung disease and worsens during pulmonary exacerbations.[111]

Exercise Therapy

Exercise tolerance has been correlated with the severity of lung disease. Higher levels of aerobic fitness in cystic fibrosis patients are associated with a lower risk of dying.[112] Decreased exercise tolerance is an important symptom that correlates with a physician's assessment of a case of pulmonary exacerbation of disease.[113] In a recent 87-adult patient study, however, maximal oxygen consumption, maximum work attained, and maximal voluntary ventilation were no better than the FEV_1 as independent correlates of mortality.[114]

Oxygen-assisted supervised training programs can improve exercise tolerance, maximal oxygen uptake, and maximal ventilation in patients with cystic fibrosis with severe pulmonary dysfunction.[115] In appropriate patients, a home exercise training program consisting of cycle training once a day has also been effective at improving exercise capacity, maximal oxygen uptake, and maximal ventilation.[116]

Employment and Cystic Fibrosis

Of 5,586 adults in the US cystic fibrosis registry reporting employment status in 1994, 54% were employed part- or full-time, 19% were students, 5% were full-time homemakers, and 22% were unemployed.[4] In a recent detailed analysis, 23 of 49 adults with cystic fibrosis said their disease had affected their career choice, yet only 9 had ever received career counseling. Adult-

diagnosed cystic fibrosis, female sex, and single marital status were independent risk factors for disability even after taking disease severity into account. This study emphasized the possible benefit of a complete vocational needs assessment for patients with this disease.[117]

In a comparative study of psychosocial assets of patients with cystic fibrosis, the occupational status attained by those who had ever entered the work force was at least as good as that attained by members of the comparison (without cystic fibrosis) group. No significant differences were seen between the persons with cystic fibrosis and the comparison group in terms of current life satisfaction and self-esteem.[118] For many young adults with this disease, timely career or job counseling is an important aspect of their comprehensive care. Often the need to retain group health insurance is an important factor in the decision about employment. The value of employment for self-image and self-worth is an important issue in considering the timing of decisions about disability.

Sexuality

The median survival for women with cystic fibrosis is 27.3 ± 3.8 years compared with 29.6 ± 2.4 years for men. The survival curves for men and women with cystic fibrosis diverge at about 10 to 15 years of age.[4] The reason for this divergence of survival curves and for the difference in mean survival is as yet unexplained.

Whereas married patients with cystic fibrosis do not differ in the degree of satisfaction with their sex lives from healthy counterparts, 38% of unmarried cystic fibrosis patients are dissatisfied with their sexual activities as compared with a healthy comparison group.[118] A diagnosis of cystic fibrosis influences women's decisions about childbearing, forcing them to weigh the desire for children against health concerns.[119]

Nearly all men with cystic fibrosis are infertile due to obstruction and degeneration of the vas deferens, and those desiring to father children should undergo semen analysis. Because women with the disease have anatomically normal reproductive tracts, their fertility rates are considerably higher. Infertility in women with this disease is due either to changes in cervical mucus leading to obstruction of the cervical os or to amenorrhea caused by malnutrition.[120] All women with cystic fibrosis who are of childbearing age and wish to avoid pregnancy should be counseled regarding the possibility of fertility.

Options for infertile men with cystic fibrosis are currently limited to artificial insemination of the partner with donor sperm or adoption, although there have been reports of modest success with epididymal sperm aspiration and subsequent artificial insemination.[121] Women with cystic fibrosis who have failed to become pregnant despite a period of unprotected intercourse with a fertile man should be tested for the use of estrogens to thin cervical mucus, given treatment directed toward correcting anovulatory cycles, or if all else fails, have direct intrauterine insemination with their partner's sperm.[122]

Since 1976, the Cystic Fibrosis Foundation has been accumulating data on the annual incidence of pregnancies among US women with the disease. In 1994, a total of 135 pregnancies were reported to the registry, 43% of which resulted in live births, and 37% were undelivered at the time of the survey. Only 10% of the pregnancies were terminated by therapeutic abortion, down from 22% in 1990.[4] The outcome of pregnancy in these women is related to a woman's pulmonary state; a low pregravid FEV_1 may suggest a worse outcome.[123] Pregnancy may impose a life-threatening burden on a pregnant woman with cystic fibrosis who has severe lung impairment. Such patients must be monitored for hypoxemia, cor pulmonale, and progressive pulmonary hypertension, and caloric intake must be increased for the fetus to gain weight appropriately.[120] Although genetic counseling should be offered to all pregnant women with cystic fibrosis, it is unknown what effect screening of the husband or fetus has on a woman's decision to complete the pregnancy.

Transplantation

Patients with cystic fibrosis should be considered for lung transplantation when they have severely reduced lung function (FEV_1 <30% of predicted) and a progressive decline in their health and quality of life. This functional decline should be unresponsive to maximal treatment, which usually includes administering supplemental oxygen. Referrals for evaluation should be made early because patients accepted as transplantation candidates may wait as long as two years for allograft transplantation at larger centers. Two-year mortality rates of greater than 50% are reported in cystic fibrosis patients with an FEV_1 of less than 30% of predicted and either a Pa_{O_2} of less than 55 mm of mercury or a Pc_{O_2} of greater than 50 mm of mercury.[124]

In 1994, bilateral lung or heart-lung transplantations were done on 96 patients in the cystic fibrosis registry, an increase from 56 patients in 1992 (Figure 2).[4] The actuarial survival of cystic fibrosis patients following lung transplantation is 60% to 85% at one and 50% to 75% at two years.[125,126] Because of the poor availability of cadaver organs, some centers have performed living-related donor lung transplantation for end-stage cystic fibrosis.[127]

Because these patients retain their native sinuses, trachea, and proximal main bronchi after lung transplantation, the organisms infecting these regions become possible sources of infection. One group from the United Kingdom, however, noted no difference in rates of infectious complications between their recipients with cystic fibrosis and those without.[128] In 62 transplantations performed in 59 patients (27 with cystic fibrosis) at the University of North Carolina at Chapel Hill between 1990 and 1993, there was no increased incidence of infectious complications among cystic fibrosis patients despite pretransplantation sputum cultures positive for *B cepacia* in 5 and *A fumigatus* in 17.[129]

Without definitive therapy for cystic fibrosis, lung transplantation remains the only option for those patients who have progressed to a state of severe pulmonary

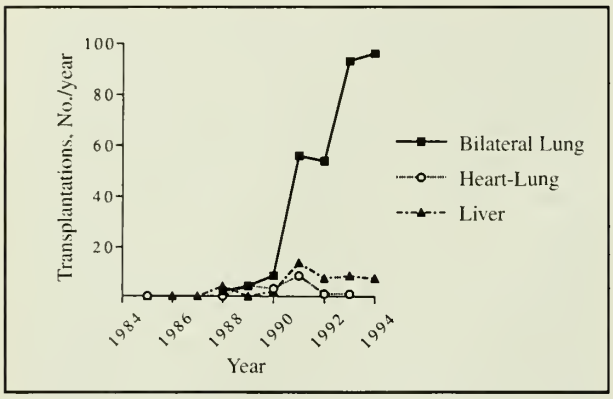

Figure 2.—The graph shows the transplantation procedures performed from 1985 to 1994 on patients with cystic fibrosis. In 1994, lung transplantations were classified as bilateral, lobar, or heart-lung combined (from Cystic Fibrosis Foundation[4]).

disability. A comprehensive review of lung transplantation for cystic fibrosis has recently been published.[130]

The Future—Gene Transfer

Within a year after the identification of *CFTR*, wild-type *CFTR* in a retrovirus vector was used to correct the cystic fibrosis defect of a human cell line in vitro.[131] In 1993, just three years later, clinical trials for *CFTR* gene transfer to humans were approved, and successful *CFTR* gene transfer to the respiratory tracts of cystic fibrosis patients was soon accomplished.[132,133] As of October 1994, more than 40 human subjects have participated in gene transfer trials in the United States, the United Kingdom, and France. A thorough account of the current state of cystic fibrosis gene transfer and the obstacles encountered was recently published.[134]

Adenovirus is tropic for respiratory lung epithelium and in theory is an elegant vector for gene transfer to the respiratory tract. Adenoassociated virus is also naturally tropic for the lung, and in the absence of a helper virus, its genome remains incorporated into the host DNA. Because of the natural tropism of these vectors, their ability to target airway cells is high.

Liposomal vectors, on the other hand, are artificial lipid vesicles that spontaneously fuse with host cell membranes to transfer DNA into a cell. There may be less inflammatory cell effect with these vectors than with viral vectors. The efficiency of the delivery of liposome vectors is high, but the expression of *CFTR* and reporter genes is low.[135] This may be due to an inefficient transport of DNA from the cytoplasm to the nucleus.[136]

Correction of the abnormal transmembrane-potential difference, *CFTR* gene expression, and normalized ion transport may be used to demonstrate the efficiency of human gene transfer.[137,138] Although these techniques are sensitive and appropriate for the study of gene transfer, it is unknown how widespread a change in potential difference or *CFTR* expression is necessary to effect objective clinical improvement. Because research into the field of gene transfer is young, no studies have yet been done with the goal of demonstrating improvements in FEV_1 or changes in the viscoelastic properties of sputum.

The targeting of gene transfer may prove to be an obstacle. The *CFTR* gene is preferentially expressed in the submucosal glands of bronchi, especially in the ducts and serous gland cells, and is expressed at only low levels in the respiratory tract surface epithelium.[11] In the distal airways, *CFTR* is not expressed in ciliated cells, but is detected in subpopulations of epithelial cells in bronchiolar-alveolar tissues.[139] All cells in the airway appear to be possible targets for *CFTR* gene transfer. It is unknown, however, whether the prolonged expression of *CFTR* in airway cells other than the submucosal glands will sufficiently correct the pathophysiologic defect and effect a change in clinical status. Questions regarding the efficiency of gene transfer to submucosal glands are beginning to be answered; human airway xenografts in immunodeficient mice have been used to demonstrate that the penetration of viral particles, rather than tropism, is particularly important for gene transfer into these gland cells.[140]

Viral vectors are also not without their adverse effects. The histologic examination of nonhuman primates receiving high-dose first-generation adenovirus vectors shows peribronchial, perivascular, and alveolar space mononuclear cell infiltrates. Measurable increases in cytokines, including interleukins-1 and -8, are detected in bronchoalveolar lavage fluid, although no changes are noted within the parenchyma. Lower doses of vector, equivalent to those experimentally used in humans, do not result in cytokine or inflammatory cell responses, although antiadenovirus antibodies develop.[141] Second-generation adenovirus vectors not containing genes encoding viral proteins may ameliorate the T-cell response, but the antibody response is produced in response to the viral proteins of the transferred viruses.[142] Thus, alterations of the vector genome may have little effect on the development of antibodies that block subsequent in vivo uptake of vector.[143] In addition to an immune response, adenoviral vectors induce a slowing of airway epithelial cell proliferation through an apparent alteration of cell cycle regulation and increase the commitment to an apoptotic death.[144] These factors help explain why *CFTR* expression in human gene transfer subjects has not been prolonged. Insertional mutagenesis is not a risk with adenovirus vectors, but is possible with adenoassociated virus vectors.[145]

Neither gene transfer to the respiratory tracts of persons with cystic fibrosis nor lung transplantation will correct the hepatobiliary disease that affects about 20% of patients[80] and is the cause of death in about 2%.[4] Successful gene transfer to the biliary epithelium has been achieved in vivo in rats using retrograde infusion through the common bile duct[146] and in vitro with human intrahepatic biliary epithelial cell lines using adenovirus vectors.[147] As has been the case with airway gene transfer, the intrahepatic biliary epithelial cells did not exhibit prolonged CFTR function.

Conclusion

Many important questions remain regarding our understanding of the *CFTR* gene and how best to transfer it into epithelial cells of relevance in patients with cystic fibrosis. It is perhaps unjustified to think that gene therapy will have a major effect on life expectancy in the near future. Meanwhile, the development of the next generation of agents that target the ion transport defect of cystic fibrosis represents an important focus. Are there other means of controlling airway surface liquid composition? Can the new sputum-active agents improve survival, or will other novel therapies directed against airway infection and inflammatory-immune processes be necessary? While we ask these and other questions, an ever-increasing population of cystic fibrosis patients is growing older, attending school, working, coping with the challenging socioeconomic problems related to their disease and to health care delivery systems, and in some cases having families. As in the 1960s, the mission of clinicians treating these patients continues to be the improvement of airway clearance and nutrition and the treatment of airway infection and inflammation. In patients with severe lung disease and the appropriate socioeconomic conditions, lung transplantation is an additional management option. Despite the remarkable advancement of the understanding of CFTR, approaches for correcting the genetic defect will continue to be challenging, with gene therapy unlikely to affect the lives of today's cystic fibrosis adults. Thus, the careful application of other supportive interventions should remain the focus of clinical care for the 1990s.

National Resources for Physicians and Patients With Cystic Fibrosis

Cystic Fibrosis Foundation
6931 Arlington Rd
Bethesda, MD 20814
(301) 951-4422
Phone: 1-800-FIGHT CF
Fax: (301) 951-6378

This is an excellent resource for patients with cystic fibrosis and their physicians. It coordinates, supports, and accredits cystic fibrosis centers nationwide and provides funds to support clinical and basic science research. An annual conference is held each October emphasizing all aspects of cystic fibrosis care.

International Association of Cystic Fibrosis Adults
Barbara L. Palys
82 Ayer Rd
Harvard, MA 01451-1409
Internet: bpalys@genesis.tiac.net

This organization is run by adults with cystic fibrosis dedicated to enhancing the exchange of information within the world's adult cystic fibrosis community. It publishes a quarterly newsletter (circulation 23,500) and organizes biennial international conferences for adults with cystic fibrosis.

Cystic Fibrosis Research, Inc
560 San Antonio Rd, Ste 103
Palo Alto, CA 94306-4349
Phone: (415) 856-0546
Fax: (415) 856-0554
Internet: cfri@netcom.com

This organization is dedicated to raising funds to support research and educational programs. It publishes educational brochures and a newsletter (circulation 13,000) and sponsors an annual educational conference and cystic fibrosis summer camp in addition to quarterly support-group meetings.

REFERENCES

1. Fanconi G, Uehlinger E, Knauer C: Das coeliakiesyndrom bei angeborener zysticher pankreasfibromatose und bronkiektasen. Wien Med Wochenschr 1936; 86:753-756

2. Anderson DH: Cystic fibrosis of the pancreas and its relation to celiac disease: Clinical and pathological study. Am J Dis Child 1938; 56:344-399

3. Matthews LW, Doershuk CF, Wise M, Eddy G, Nudelman H, Spector S: A therapeutic regimen for patients with cystic fibrosis. J Pediatr 1964; 65: 558-575

4. Patient Registry 1994 Annual Data Report. Bethesda, Md, Cystic Fibrosis Foundation, August 1995

5. Wilson JM: Prospects for Human Gene Therapy for Cystic Fibrosis. Plenary session, Eighth Annual North American Cystic Fibrosis Conference, Orlando, Fla, October 1994

6. Eiberg H, Mohr J, Schmiegelow K, Nielsen LS, Williamson R: Linkage relationships of paraoxinase (PON) with other markers: Evidence of PON-cystic fibrosis synteny. Clin Genet 1985; 28:265-271

7. Tsui LC, Buchwald M, Barker D, et al: Cystic fibrosis locus defined by a genetically linked polymorphic marker. Science 1985; 230:1054-1057

8. Rommens JM, Ianuzzi MC, Kerem BS, et al: Identification of the cystic fibrosis gene: Chromosome walking and jumping. Science 1989; 245:1059-1065

9. Riordan JR, Rommens JM, Kerem BS, et al: Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 1989; 245:1066-1072

10. Kerem BS, Rommens JM, Buchanan JA, et al: Identification of the cystic fibrosis gene: Genetic analysis. Science 1989; 245:1073-1080

11. Engelhardt JF, Yankaskas JR, Ernst SA: Submucosal glands are the predominant site of CFTR expression in the human bronchus. Nature Genet 1992; 2:240-248

12. Crawford I, Maloney P, Zeitlin PL, et al: Immunocytochemical localization of the cystic fibrosis gene product CFTR. Proc Natl Acad Sci USA 1991; 88:9262-9266

13. Cohn JA, McGill J, Basavappa S, Kole J, Fitz JG: Bile duct epithelial cells are the predominant site of CFTR in liver. Pediatr Pulmonol Suppl 1992; 8:249

14. Miller PW: CFTR mutations and adult pulmonary diseases. Pediatr Pulmonol Suppl 1994; 10:137

15. Zielenski J, Tsui LC: Cystic fibrosis genotype and phenotype variations. Annu Rev Genet 1995; 29:777-807

16. Cystic Fibrosis Genetic Analysis Consortium: Population variation of common cystic fibrosis mutations. Hum Mutat 1994; 4:167-177

17. Gadsby DC, Nairn AC: Regulation of CFTR channel gating. Trends Biochem Sci 1994; 19:513-518

18. Gabriel SE, Brigman KN, Koller BH, Boucher RC, Stutts MJ: Cystic fibrosis heterozygote resistance to cholera toxin in the cystic fibrosis mouse model. Science 1994; 266:107-109

19. Goldstein JL, Sahi J, Bhuva M, Layden TJ, Rao MC: *Escherichia coli* heat-stable enterotoxin-mediated colonic Cl– secretion is absent in cystic fibrosis. Gastroenterology 1994; 107: 950-956

20. Tsui LC: The cystic fibrosis transmembrane conductance regulator gene. Am J Respir Crit Care Med 1995; 151:S47-S53

21. Welsh MJ, Smith AE: Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. Cell 1993; 73:1251-1254

22. Knowles MR, Gatzy J, Boucher R: Increased bioelectric potential difference across respiratory epithelia in cystic fibrosis. N Engl J Med 1981; 305:1489-1495

23. Boucher RC: Human airway ion transport (pt 1). Am J Respir Crit Care Med 1994; 150:271-281

24. Boucher RC: Human airway ion transport (pt 2). Am J Respir Crit Care Med 1994; 150:581-593

25. Burch LH, Talbot CR, Knowles MR, Canessa CM, Rossier BC, Boucher RC: Relative expression of the human epithelial Na^+ channel subunits in normal and cystic fibrosis airways. Am J Physiol 1995; 269:C511-C518

26. Stutts MJ, Canessa CM, Olsen JC, et al: CFTR as a cAMP-dependent regulator of sodium channels. Science 1995; 269:847-850

27. Schwiebert EM, Egan ME, Hwang TH, et al: CFTR regulates outwardly rectifying chloride channels through an autocrine mechanism involving ATP. Cell 1995; 81:1063-1073

28. Hamosh A, Corey M, and the Cystic Fibrosis Genotype-Phenotype Consortium: Correlation between genotype and phenotype in cystic fibrosis. N Engl J Med 1993; 329:1308-1313

29. Denning GM, Ostedgaard LS, Welsh MJ: Abnormal localization of cystic fibrosis transmembrane conductance regulator in primary cultures of cystic fibrosis airway epithelia. J Cell Biol 1992; 118:551-559

30. Sheppard DN, Rich DP, Ostedgaard LS, Gregory RJ, Smith AE, Welsh MJ: Mutations in CFTR associated with mild disease form Cl– channels with altered pore properties. Nature 1993; 362:160-164

31. Imundo L, Barasch J, Prince A, Al-Awqati Q: Cystic fibrosis epithelial cells have a receptor for pathogenic bacteria on their apical surface. Proc Natl Acad Sci USA 1995; 92:3019-3023

32. Warner JO: Immunology of cystic fibrosis. Br Med Bull 1992; 48: 893-911

33. Roussey M, Lamarre A, Marcotte JE, et al: Pulmonary function and clinical course in 252 CF patients after colonization with *Pseudomonas aeruginosa* (pa), *cepacia* and *Xanthomonas maltophilia*. Pediatr Pulmonol Suppl 1994; 10:253

34. Schuster A, Fahy JV, Ueki I, Nadel JA: Cystic fibrosis sputum induces a secretory response from airway gland serous cells that can be prevented by neutrophil protease inhibitors. Eur Respir J 1995; 8:1-14

35. Widdicombe JH: Accumulation of airway mucus in cystic fibrosis. Pulmon Pharmacol 1994; 7:225-233

36. Regnis JA, Robinson M, Bailey DL, et al: Mucociliary clearance in patients with cystic fibrosis and in normal subjects. Am J Respir Crit Care Med 1994; 150:66-71

37. Dupuit F, Kälin N, Brézillon S, Hinnrasky J, Tümmler B, Puchelle E: CFTR and differentiation markers expression in non-CF and ΔF508 homozygous CF nasal epithelium. J Clin Invest 1995; 96:1601-1611

38. Hingley ST, Hastie AT, Kueppers F, Higgins ML, Weinbaum G, Shryock T: Effect of ciliostatic factors from *Pseudomonas aeruginosa* on rabbit respiratory cilia. Infect Immun 1986; 51:254-262

39. Fick RB, Baltimore RS, Squier SV, Reynolds HY: IgG proteolytic activity of *Pseudomonas aeruginosa* in cystic fibrosis. J Infect Dis 1985; 151:589-598

40. Wood DE, To M, Sohol PA: *Pseudomonas aeruginosa* exoenzymes as a pathogenic determinant in respiratory infections. Antibiot Chemother 1989; 42:27-35

41. Nelson JW, Tredgett MW, Sheehan JK, Thornton DJ, Notman D, Govan JRW: Mucinophilic and chemotactic properties of *Pseudomonas aeruginosa* in relation to pulmonary colonization in cystic fibrosis. Infect Immun 1990; 58:1489-1495

42. Govan JRW, Nelson JW: Microbiology of lung infection in cystic fibrosis. Br Med Bull 1992; 48:912-930

43. Speert DP, Farmer SW, Campbell ME, Musser JM, Selander RK, Kuo S: Conversion of *Pseudomonas aeruginosa* to the phenotype characteristic of strains from patients with cystic fibrosis. J Clin Microbiol 1990; 28:188-194

44. Zielinski NA, Maharaj R, Roychoudhury S, Danganan C, Hendrickson W, Chakrabarty AM: Alginate synthesis in *Pseudomonas aeruginosa*: Environmental regulation of the algC promoter. J Bacteriol 1992; 174:7680-7688

45. Lam J, Chan R, Lam K, Costerton JW: Production of mucoid microcolonies by *Pseudomonas aeruginosa* within infected lungs in cystic fibrosis. Infect Immun 1980; 28:546-556

46. Bruce MC, Poncz L, Klinger JD, Stern RC, Tomashefski JF Jr, Dearborn DG: Biochemical and pathologic evidence for proteolytic destruction of lung connective tissue in cystic fibrosis. Am Rev Respir Dis 1985; 132:529-535

47. Konstan MW, Hilliard KA, Norvell TM, Berger M: Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. Am J Respir Crit Care Med 1994; 150:448-454

48. Birrer P, McElvaney NG, Rudeberg A, et al: Protease-antiprotease imbalance in the lungs of children with cystic fibrosis. Am J Respir Crit Care Med 1994; 150:207-213

49. Kilby JM, Gilligan PH, Yankaskas JR, Highsmith WE Jr, Edwards LJ, Knowles MR: Nontuberculous mycobacteria in adult patients with cystic fibrosis. Chest 1992; 102:70-75

50. Pegues DA, Carson LA, Tablan OC, et al, and the Summer Camp Study Group: Acquisition of *Pseudomonas cepacia* at summer camps for patients with cystic fibrosis. J Pediatr 1994; 124:694-702

51. Steinbach S, Sun L, Jiang RZ, et al: Transmissibility of *Pseudomonas cepacia* infection in clinic patients and lung-transplant recipients with cystic fibrosis. N Engl J Med 1994; 331:981-987

52. Lindsey CA, Bosso JA: Optimisation of antibiotic therapy in cystic fibrosis patients. Clin Pharmacokinet 1993; 24:496-506

53. Mannes GPM, van Aalderen WMC, Manson WL: Tobramycin in a single daily dose in adult CF patients. Pediatr Pulmonol Suppl 1994; 10:259

54. Vic P, Ategbo S, Turck D, et al: Efficacy and tolerance of once-daily amikacin (AM) in cystic fibrosis (CF) patients. Pediatr Pulmonol Suppl 1994; 10:251

55. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL: Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 1985; 132:761-765

56. van Aalderen WMC, Mannes GPM, Bosma ES, Roorda RJ, Heymans HSA: Home care in cystic fibrosis patients. Eur Respir J 1995; 8:172-175

57. Pleasants RA, Walker TR, Samuelson WM: Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. Chest 1994; 106:1124-1128

58. Ramsey BW, Dorkin HL, Eisenberg JD, et al: Efficacy of aerosolized tobramycin in patients with cystic fibrosis. N Engl J Med 1993; 328:1740-1746

59. Steinkamp G, Tümmler B, Gappa M, et al: Longterm tobramycin aerosol therapy in cystic fibrosis. Pediatr Pulmonol 1989; 6:91-98

60. MacLusky IB, Gold R, Corey M, Levison H: Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. Pediatr Pulmonol 1989; 7:42-48

61. Smith JA: Neutrophils, host defense, and inflammation: A double-edged sword. J Leukoc Biol 1994; 56:672-686

62. Auerbach HS, Kirkpatrick JA, Williams M, Colten HR: Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. Lancet 1985; 2:686-688

63. Eigen H, Rosenstein BJ, FitzSimmons S, Schidlow DV, and the Cystic Fibrosis Foundation Prednisone Trial Group: A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. J Pediatr 1995; 126: 515-523

64. Konstan MW, Byard PJ, Hoppel CL, Davis PB: Effect of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med 1995; 332:848-854

65. Aronoff SC, Quinn FJ, Carpenter LS, Novick WJ: Effects of pentoxifylline on sputum neutrophil elastase and pulmonary function in patients with cystic fibrosis: Preliminary observations. J Pediatr 1994; 125:992-997

66. Rees DD, Brain JD: Effects of cystic fibrosis airway secretions on rat lung: Role of neutrophil elastase. Am J Physiol 1995; 269:L195-L202

67. Cryz SJ Jr, Wedgwood J, Lang AB, et al: Immunization of noncolonized cystic fibrosis patients against *Pseudomonas aeruginosa*. J Infect Dis 1994; 169:1159-1162

68. Durie PR, Pencharz PB: Nutritional deficiencies in cystic fibrosis. Br Med Bull 1992; 48:823-847

69. Kraisinger M, Hochhaus G, Stecenko A, Bowser E, Hendeles L: Clinical pharmacology of pancreatic enzymes in patients with cystic fibrosis and in vitro performance of microencapsulated formulations. J Clin Pharmacol 1994; 34:158-166

70. Smyth RL, Van Aelzen D, Smyth AR, Lloyd DA, Heaf DP: Strictures of the ascending colon in cystic fibrosis and high-strength pancreatic enzymes. Lancet 1994; 343:85-86

71. MacSweeney EJ, Oades PJ, Buchdahl R, Rosenthal M, Bush A: Relation of thickening of colon wall to pancreatic-enzyme treatment in cystic fibrosis. Lancet 1995; 345:752-756

72. Corey M, McLaughlin FJ, Williams M, Levison H: A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 1988; 41:583-591

73. Ramsey BW, Farrel PM, Pencharz P, and the Consensus Committee: Nutritional assessment and management in cystic fibrosis: A consensus report. Am J Clin Nutr 1992; 55:108-116

74. Homnick DN, Cox JH, DeLoof MJ, Ringer TV: Carotenoid levels in normal children and in children with cystic fibrosis. J Pediatr 1993; 122(pt 1): 703-707

75. Winklhofer-Roob BM, Puhl H, Khoschsorur G, van't Hof MA, Esterbauer H, Shmerling DH: Enhanced resistance to oxidation of low density lipoproteins and decreased lipid peroxide formation during β-carotene supplementation in cystic fibrosis. Free Radic Biol Med 1995; 18:849-859

76. Gorlin R: The biological actions and potential clinical significance of dietary omega-3 fatty acids. Arch Intern Med 1988; 148:2043-2048

77. Konstan MW, Walenga RW, Hilliard KA, Berger M: Eicosanoid content of bronchoalveolar lavage fluid is markedly elevated in cystic fibrosis. Pediatr Pulmonol Suppl 1991; 6:302

78. Henderson WR Jr, Astley SJ, McCready MM, et al: Oral absorption of omega-3 fatty acids in patients with cystic fibrosis who have pancreatic insufficiency and in healthy control subjects. J Pediatr 1994; 124:400-408

79. O'Brien S, Keogan M, Casey M, et al: Biliary complications of cystic fibrosis. Gut 1992; 33:387-391

80. Colombo C, Apostolo MG, Ferrari M, et al: Analysis of risk factors for the development of liver disease associated with cystic fibrosis. J Pediatr 1994; 124:393-399

81. Waters DL, Dorney SFA, Gruca MA, et al: Hepatobiliary disease in cystic fibrosis patients with pancreatic sufficiency. Hepatology 1995; 21:963-969

82. Feigelson J, Anagnostopoulos C, Poquet M, Pecau Y, Munck A, Navarro J: Liver cirrhosis in cystic fibrosis—Therapeutic implications and long-term follow up. Arch Dis Child 1993; 68:653-657

83. Galabert C, Montet JC, Lengrand D, et al: Effects of ursodeoxycholic acid on liver function in patients with cystic fibrosis and chronic cholestasis. J Pediatr 1992; 121:138-141

84. Borowitz D: Pathophysiology of gastrointestinal complications of cystic fibrosis. Semin Respir Crit Care Med 1994; 15:391-401

85. Neglia JP, FitzSimmons SC, Maisonneuve P, et al, and the Cystic Fibrosis and Cancer Study Group: The risk of cancer among patients with cystic fibrosis. N Engl J Med 1995; 332:494-499

86. Patterson JM, Budd J, Goetz D, Warwick WJ: Family correlates of a 10-year pulmonary health trend in cystic fibrosis. Pediatrics 1993; 91:383-389

87. Williams MT: Chest physiotherapy and cystic fibrosis—Why is the most effective form of treatment still unclear? Chest 1994; 106:1872-1882

88. Miller S, Hall D, Clayton CB, Nelson R: Chest physiotherapy in cystic fibrosis (CF) a comparative study of autogenic drainage (AD) and active cycle of breathing technique (ACBT) (formerly FET). Pediatr Pulmonol Suppl 1993; 9:267

89. Hofmeyr JL, Webber BA, Hodson ME: Evaluation of positive pressure as an adjunct to chest physiotherapy in the treatment of cystic fibrosis. Thorax 1986; 41:951-954

90. Konstan MW, Stern RC, Doershuk CF: Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. J Pediatr 1994; 124: 689-693

91. Arens R, Gozal D, Omlin KJ, et al: Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. Am J Respir Crit Care Med 1994; 150:1154-1157

92. George RJD, Pavia D, Woodman G, et al: Oral high frequency oscillation (OHFO) as an adjunct to physiotherapy (PHYSIO) in cystic fibrosis (CF). Thorax 1986; 41:235P

93. Thomas J, Cook DJ, Brooks D: Chest physical therapy management of patients with cystic fibrosis. Am J Respir Crit Care Med 1995; 151:846-850

94. Smith AL, Redding G, Doershuk C, et al: Sputum changes associated with therapy for endobronchial exacerbation in cystic fibrosis. J Pediatr 1988; 112:547-554

95. Shak S, Capon DJ, Hellniss R, Marsters SA, Baker CL: Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 1990; 87:9188-9192

96. Fuchs HJ, Borowitz DS, Christiansen DH, et al: Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med 1994; 331:637-642

97. Rosenstein BJ, Johnson CAC, for the rhDNase Phase III Study Group: Long-term follow-up of Phase III rhDNase trial. Pediatr Pulmonol Suppl 1994; 10:113-114

98. Vasconcellos CA, Allen PG, Wohl ME, Drazen JM, Janmey PA, Stossel TP: Reduction in viscosity of cystic fibrosis sputum in vitro by gelsolin. Science 1994; 263:969-971

99. Knowles MR, Olivier KN, Bennett W, et al: Aerosolized uridine triphosphate (UTP) + amiloride: Safety and effect on mucociliary clearance in normal subjects and CF patients. Pediatr Pulmonol Suppl 1994; 10:99-100

100. Stafanger G, Koch C: *N*-Acetylcysteine in cystic fibrosis and *Pseudomonas aeruginosa* infection: Clinical score, spirometry and ciliary motility. Eur Respir J 1989; 2:234-237

101. Stafanger G, Garne S, Howitz P, Morkassel E, Koch C: The clinical effect and the effect on the ciliary motility of oral *N*-acetylcysteine in patients with cystic fibrosis and primary ciliary dyskinesia. Eur Respir J 1988; 1:161-167

102. Schidlow DV, Taussig LM, Knowles MR: Cystic Fibrosis Foundation consensus report on pulmonary complications of cystic fibrosis. Pediatr Pulmonol 1993; 15:187-198

103. Mroueh S, Spock A: Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Chest 1994; 105:32-36

104. Hutcheson PS, Rejent AJ, Slavin RG: Variability in parameters of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. J Allergy Clin Immunol 1991; 88:390-394

105. Shale DJ, Faux JA, Lane DJ: Trial of ketoconazole in non-invasive pulmonary aspergillosis. Thorax 1987; 42:26-31

106. Slavin RG: Medical management of nasal polyps and sinusitis. J Allergy Clin Immunol 1991; 88:141-146

107. Ramsey B, Richardson MA: Impact of sinusitis in cystic fibrosis. J Allergy Clin Immunol 1992; 90:547-552

108. Sharma GD, Doershuk CF, Stern RC: Erosion of the wall of the frontal sinus caused by mucopyocele in cystic fibrosis. J Pediatr 1994; 124:745-747

109. Stern RC, Boat TF, Wood RE, Matthews LW, Doershuk CF: Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child 1982; 136:1067-1070

110. Cepero R, Smith RJH, Catlin FI, Bressler KL, Furuta GT, Shandera KC: Cystic fibrosis—An otolaryngologic perspective. Otolaryngol Head Neck Surg 1987; 97:356-360

111. Johnson S, Knox AJ: Arthropathy in cystic fibrosis. Respir Med 1994; 88:567-570

112. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF: The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 1992; 327:1785-1788

113. Ramsey B, Pepe M, Warren JW: Pulmonary exacerbation—How do we define it? Pediatr Pulmonol Suppl 1994; 10:77-78

114. Moorcroft AJ, Dodd ME, Webb AK: Exercise testing and prognosis in adult cystic fibrosis. Pediatr Pulmonol Suppl 1994; 10:265

115. Heijerman HGM, Bakker W, Sterk PJ, Dijkman JH: Oxygen-assisted exercise training in adult cystic fibrosis patients with pulmonary limitation to exercise. Int J Rehabil Res 1991; 14:101-115

116. de Jong W, Grevink RG, Roorda RJ, Kaptein AA, van der Schans CP: Effect of a home exercise training program in patients with cystic fibrosis. Chest 1994; 105:463-468

117. Gillen M, Lallas D, Brown C, Yelin E, Blanc P: Work disability in adults with cystic fibrosis. Am J Respir Crit Care Med 1995; 152:153-156

118. Shepherd SL, Hovell MF, Harwood IR, et al: A comparative study of the psychosocial assets of adults with cystic fibrosis and their healthy peers. Chest 1990; 97:1310-1316

119. Burke W, McDonald GJ, Aitken ML: Reproductive decision-making in women affected with CF. Pediatr Pulmonol Suppl 1994; 10:292

120. Kotloff RM: Reproductive issues in patients with cystic fibrosis. Semin Respir Crit Care Med 1994; 15:402-413

121. Silber SJ, Ord T, Balmaceda J, Patrizio P, Asch RH: Congenital absence of the vas deferens—The fertilizing capacity of human epididymal sperm. N Engl J Med 1990; 323:1788-1792

122. Kredentser JV, Podrant C, McCoshen JA: Intrauterine insemination for infertility due to cystic fibrosis. Fertil Steril 1986; 45:425-426

123. Edenborough FP, Stableforth DE, Webb AK, Mackenzie WE, Smith DL: Outcome of pregnancy in women with cystic fibrosis. Thorax 1995; 50: 170-174

124. Kerem E, Reisman J, Corey M, Canny GJ, Levison H: Prediction of mortality in patients with cystic fibrosis. N Engl J Med 1992; 326:1187-1191

125. Tamm M, Higenbottam T: Heart-lung and lung transplantation for cystic fibrosis: World experience. Semin Respir Crit Care Med 1994; 15:414-425

126. Egan TM, Detterbeck FC, Mill MR, et al: Improved results of lung transplantation for patients with cystic fibrosis. J Thorac Cardiovasc Surg 1995; 109:224-235

127. Starnes VA, Barr ML, Cohen RG, Schenkel FA, and the USC Transplant Group: Living related lung transplantation in cystic fibrosis. Pediatr Pulmonol Suppl 1994; 10:128-129

128. de Leval MR, Smith R, Whitehead B, et al: Heart and lung transplantation for terminal cystic fibrosis. J Thorac Cardiovasc Surg 1991; 101:633-642

129. Flume PA, Egan TM, Paradowski LJ, Detterbeck FC, Thompson JT, Yankaskas JR: Infectious complications of lung transplantation—Impact of cystic fibrosis. Am J Respir Crit Care Med 1994; 149:1601-1607

130. Kotloff RM, Zukerman JB: Lung transplantation for cystic fibrosis: Special considerations. Chest 1996; 109:787-798

131. Drumm ML, Pope HA, Cliff WH, et al: Correction of the cystic fibrosis defect in vitro by retrovirus-mediated gene transfer. Cell 1990; 62:1227-1233

132. Zabner J, Couture LA, Gregory RJ, Graham SM, Smith AE, Welsh MJ: Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. Cell 1993; 75:207-216

133. Crystal RG, McElvaney NG, Rosenfeld MA, et al: Administration of an adenovirus containing the human CFTR cDNA to the respiratory tract of individuals with cystic fibrosis. Nature Genet 1994; 8:42-51

134. Rosenfeld MA, Collins FS: Gene therapy for cystic fibrosis. Chest 1996; 109:241-252

135. Bebok A, Dong JY, Logan JJ, et al: Plasmid delivery is not a limiting factor using lipid mediated gene transfer in vitro. Pediatr Pulmonol Suppl 1994; 10:223

136. Zabner J, Fasbender A, Moninger T, Welsh MJ: Evaluation of cationic lipids for gene transfer. Pediatr Pulmonol Suppl 1994; 10:223

137. Wilson JM: Cystic fibrosis: Strategies for gene therapy. Semin Respir Crit Care Med 1994; 15:439-445

138. Johnson LG, Boyles SE, Wilson J, Boucher RC: Normalization of raised sodium absorption and raised calcium-mediated chloride secretion by adenovirus-mediated expression of cystic fibrosis transmembrane conductance regulator in primary human cystic fibrosis airway epithelial cells. J Clin Invest 1995; 95:1377-1382

139. Engelhardt JF, Zepeda M, Cohn JA, Yankaskas JR, Wilson JM: Expression of the cystic fibrosis gene in adult human lung. J Clin Invest 1994; 93:737-749

140. Pilewski JM, Engelhardt JF, Bavaria JE, Kaiser LR, Wilson JM, Albelda SM: Adenovirus-mediated gene transfer to human bronchial submucosal glands using xenografts. Am J Physiol 1995; 268:L657-L665

141. Yei S, Mittereder N, Whitsett JA, Wilmott R, Trapnell BC: The role of the host response in adenovirus vector-mediated gene therapy for cystic fibrosis lung disease: Toxicology and pharmacokinetics. Pediatr Pulmonol Suppl 1994; 10:151-152

142. McCoy RD, Davidson BL, Roessler BJ, et al: Pulmonary inflammation induced by incomplete or inactivated adenoviral particles. Hum Gene Ther 1995; 6:1553-1560

143. Wilson JM: Gene therapy for cystic fibrosis lung disease with recombinant adenoviruses: Host-vector interactions. Pediatr Pulmonol Suppl 1994; 10:155

144. Teramoto S, Johnson LG, Huang W, Leigh MW, Boucher RC: Adenoviral vector infection inhibits human airway epithelial cell proliferation reflecting apoptosis and alteration of the cell cycle. Pediatr Pulmonol Suppl 1994; 10:222-223

145. Kearns W, Afiore S, Cutting G, Carter B, Pearson P, Flotte T: AAV-CFTR vectors integrate at multiple chromosomal sites in a CF bronchial epithelial cell line. Pediatr Pulmonol Suppl 1993; 9:242

146. Yang Y, Raper SE, Cohn JA, Engelhardt JF, Wilson JM: An approach for treating the hepatobiliary disease of cystic fibrosis by somatic gene transfer. Proc Natl Acad Sci USA 1993; 90:4601-4605

147. Grubman SA, Fang SL, Mulberg AE, et al: Correction of the cystic fibrosis defect by gene complementation in human intrahepatic biliary epithelial cell lines. Gastroenterology 1995; 108:584-592

* * *

THE ATTENDANT

The Demerol holds her in its cool clasp.
She snorts, then starts,
as if someone else in the bed made the sound.
I watch her sleep and see her dream.
She talks, her eyebrows raised—
then frowns, arguing
against what's done.
I see how temperament
is not a veneer,
but rather lies in the grain of the wood,
set down in good and bad times.

At the very last, the personality will be present,
insistent on saying its piece.
And the sweet soul,
tolerant to the end,
will let it have that say—
then calmly will rise
to tuck in the covers,
and bend to kiss the fevered cheek.

KAREN KESKINEN©
Turlock, California

Endemic Mycosis Complicating Human Immunodeficiency Virus Infection

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Persons infected with the human immunodeficiency virus are prone to the development of many fungal diseases. Normal hosts with intact immunity usually recover from infection by these less-invasive fungi. In persons with compromised T-cell–mediated immunity, however, widespread dissemination from a pulmonary focus occurs. In this review, we discuss the epidemiology, clinical manifestations, diagnosis, and treatment of the three major North American mycoses, histoplasmosis, blastomycosis, and coccidioidomycosis. In most cases, amphotericin B is the initial drug of choice, followed by one of the azoles for lifelong maintenance therapy.

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Among many thousands of fungi existing in nature, fewer than 100 have been associated with human illness. Most of these cause disease only on the skin because this organ, with its large surface area, has the greatest environmental contact with these organisms. The second great contact between humans and the environment are the lungs. A large number of fungal spores are inhaled daily, but clinical illness produced by these organisms is uncommon.

Fungal diseases can be divided into two broad groups: diseases caused by normally pathogenic fungi, and a second group caused by fungi of lesser invasiveness that produce disease only in hosts whose immune defenses have been compromised. The pathogenic fungi include the four major endemic mycoses, histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis, that cause disease in their respective endemic areas. Cryptococcosis, the fifth major pathogenic fungal disease, is distributed worldwide. Other fungal diseases have recently come to medical attention, but their relative rarity and their poorly understood ecologic niche prevent a more thorough discussion at this time. Such a fungus is *Penicillium marneffei*, recently described in Thailand and other countries in Southeast Asia.

The endemic mycoses share a single important feature. If their infecting particles are not cleared by nonspecific host defenses, they convert to an invasive or tissue phase that is resistant to killing by nonimmune phagocytes, both neutrophils (polymorphonuclear [PMN]) and macrophages.[1] In the United States, histoplasmosis,[2] blastomycosis,[3] and coccidioidomycosis[4,5] are common, whereas paracoccidioidomycosis exists exclusively in South and Central America and will not be discussed further.[6]

These endemic mycoses cause infection in any nonimmune host; the eventual control and elimination of the fungi require the development of specific T-cell–mediated immunity. Normal hosts with intact T-cell–mediated immunity usually recover from primary infection by any of these fungi, unless the infecting dose is overwhelming.[3-8]

Opportunistic invasive fungal infections, which include aspergillosis, pseudallescheriasis, and mucormycosis, are caused by fungi that are ubiquitous in nature. Unlike spores of normally pathogenic fungi that cannot be killed by nonimmune phagocytosis, inhaled spores of the opportunistic fungi are easily dealt with by PMNs and alveolar macrophages.[1] Progressive infection by these fungi takes place only when the number or function of these phagocytes is impaired.[9,10] Although disturbances of T-cell–mediated immunity also play a role in allowing systemic infections to occur, these infections are rare even in patients with profoundly altered T-cell–mediated immunity, unless there is a concomitant alteration in the number or function of PMNs and macrophages.[11] Thus, invasive disease produced by these fungi seldom develops in patients infected with the human immunodeficiency virus (HIV).[12] Most HIV-infected patients in whom invasive aspergillosis develops have substantial alterations in PMN number and function, although a few patients have been described who have no obvious phagocyte defect.[13] Diseases caused by these organisms will not be dealt with in this article, nor will we discuss infection with *Candida* species. Mucosal infection with *Candida* species (controlled by T-cell–mediated immunity) is extremely

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
BAL = bronchoalveolar lavage
CF = complement fixation
HIV = human immunodeficiency virus
HPA = histoplasma polysaccharide antigen
PMN = polymorphonuclear neutrophil

common in patients with the acquired immunodeficiency syndrome (AIDS), but deep invasion (controlled by phagocytes) is remarkably uncommon.

The three major endemic mycoses of North America, histoplasmosis, blastomycosis, and coccidioidomycosis, share a number of features. All are soil organisms; human infection occurs when the fungal spores are inhaled. For the vast majority of patients, the portal of entry is the lungs. All three organisms are dimorphic. They grow in nature as hyphae, and the infecting spores are small, ideally sized to reach the terminal alveoli. *Histoplasma capsulatum* and *Blastomyces dermatitidis* are thermal dimorphs. After entering a mammalian host with an average body temperature of 37°C (98.6°F), the inhaled spores promptly convert to their tissue-invasive phase, which are single budding yeasts. *Coccidioidomyces immitis* is also a dimorphic organism, but in this instance the invasive phase is a giant spherule, rather than a single budding yeast. The change of form is not mediated by temperature alone, and the organism is sometimes called a tissue dimorph.

The primary pulmonary infection of these fungi in nonimmunocompromised hosts is usually a self-limited disease. Only when specific T-cell–mediated immunity is depressed do these organisms become highly invasive, resulting in widespread dissemination from a pulmonary focus.

The endemic mycoses exist in well-defined geographic areas. Histoplasmosis exists in the south-central United States, especially along major rivers.[2] Blastomycosis is coendemic over most of this area, but extends further north to include Wisconsin, Minnesota, and adjacent Canadian provinces.[3] This organism also is concentrated along waterways. Coccidioidomycosis is endemic in the desert Southwest, roughly corresponding to the area of the Lower Sonoran Life Zone. This area, as high as 1,067 m (3,500 ft) elevation, is the home of the fungus. Geographically this area encompasses west Texas, parts of New Mexico, the desert part of Arizona, and the southern part of the Central Valley of California. In addition, adjacent areas of northern Mexico are also highly endemic.[4,5]

The histopathology of the primary infection is different among the various fungi. The histopathology of histoplasmosis is primarily granulomatous, without a PMN infiltrate.[7] Primary lesions of blastomycosis and coccidioidomycosis are usually pyogranulomatous. In addition to granulomas, PMNs persist in greater or lesser numbers during active infection.[3-5]

Histoplasmosis in the Acquired Immunodeficiency Syndrome

Following the inhalation of the infecting spores, an area of pneumonitis develops, usually in the better-ventilated lower zones of the lung. During the preimmune phase of the infection, the organism gains access to the circulation through the lymphatics and disseminates widely throughout the body, where it is taken up by cells of the reticuloendothelial system. With the development of cell-mediated immunity, the now "armed" macrophages are able to kill the ingested fungi, leading to the production of granulomas and eventually healing by fibrosis.[7] It is easy to understand why in patients whose T-cell–mediated immunity has been altered by HIV infection, progressive dissemination by *H capsulatum* is especially prone to develop.

The primary infection in normal hosts is usually a self-limited illness. The acute phase of the illness frequently presents with influenza-like symptoms, but the patient recovers quickly. Sputum production is uncommon, and the vast majority of infected persons never come to medical attention due to rapid spontaneous recovery. In patients with far-advanced HIV infection, unchecked progressive dissemination takes place that may kill the host.

Progressive Disseminated Histoplasmosis

Progressive disseminated histoplasmosis may take two different forms. In adults with immunosuppression not due to AIDS and young children, there is poor granuloma formation in response to the infection.[14] The organism rapidly proliferates. This form of the disease mimics lepromatous leprosy. Because of its propensity to infect young children, this form of disseminated histoplasmosis has been referred to as the "infantile" form of the disease. In older patients, progressive disseminated histoplasmosis is a disease with a much slower pace; granulomas are well formed throughout, and only a rare organism may be seen.[14] This form of the disease has been compared with the tuberculous form of leprosy. Even before the onset of the HIV pandemic, the infantile form of progressive disseminated histoplasmosis was seen almost exclusively in immunologically altered patients, especially in persons receiving high-dose glucocorticoids or immunosuppressive therapy by cytotoxic agents.[15,16] The pace of the disease is rapid due to the unchecked proliferation of a large number of histoplasma yeasts.

Progressive disseminated histoplasmosis was reported in HIV-infected patients as early as 1981,[17] but it was not until 1987, following the reports of an increasing number of cases of the disease in HIV-infected patients, that it was accepted as an AIDS-defining illness.[18] Clinically and histopathologically, progressive disseminated histoplasmosis in patients with AIDS resembles the infantile form of the disease.

Progressive Disseminated Histoplasmosis in the Acquired Immunodeficiency Syndrome

Epidemiology

Unlike the primary form of histoplasmosis, which occurs either sporadically or in point-source outbreaks in the recognized endemic area, progressive disseminated histoplasmosis in AIDS has been described both within the endemic area and with increasing frequency outside the endemic area. Early reports first drew attention to the association of HIV infection with this disease in heavily endemic parts of the United States.[19,20] Shortly after, however, a number of reports appeared in the literature describing cases of the disease in areas of the United States not considered endemic. Careful epidemiologic investigation of the involved patients revealed that all had previously resided in areas known to be endemic for histoplasmosis.[21] On the East Coast of the United States, most patients with progressive disseminated histoplasmosis and AIDS had previously resided in Puerto Rico and other Caribbean islands, whereas on the West Coast, most had resided previously in the Midwest and south-central United States. The incidence of the disease in AIDS is highly variable from location to location. From series described from Dallas[22] and Houston,[23] on the fringes of the recognized endemic area, the dual infection occurs in about 5% of patients known to have AIDS. In more heavily endemic areas of the United States, such as Indianapolis, Indiana, progressive disseminated histoplasmosis has developed in a much larger percentage of AIDS patients. In one report, the disease was described in 27% of such patients.[24] By comparison, cryptococcal meningitis involves 6% to 10% of AIDS patients throughout the United States.[25]

Pathophysiology

The ongoing epidemic of histoplasmosis in Indianapolis has shown that when HIV-infected patients come in contact with the fungus for the first time, widespread disseminated disease will occur.[24] On the other hand, patients with disseminated histoplasmosis diagnosed in nonendemic areas who uniformly give a past history of residence in endemic areas likely are reactivating latent disease from remote exposure.[21] Further supporting the concept of endogenous reactivation in these patients is that in many the chest radiograph is normal during the initial presentation of the disease.[26]

Clinical Manifestations

The clinical presentation of progressive disseminated histoplasmosis complicating AIDS is nonspecific. It is similar to many other opportunistic infections complicating the course of HIV infection. In published reviews of the disease in patients with AIDS, fever and weight loss were the most common symptoms, occurring in about 75% of patients.[24,26] Physical examination is frequently unrevealing, although hepatosplenomegaly may occur in as much as 25% of patients.[24,26] Lymphadenopathy may occur in a small fraction. Routine laboratory test results are also nonspecific, although many patients show anemia, leukopenia, and thrombocytopenia. All of these cytopenias are frequently seen in patients receiving zidovudine therapy. The chest radiograph at presentation may range from normal to diffuse reticulonodular infiltrates.[26] Ultimately, virtually all patients show a diffuse reticulonodular picture. Respiratory symptoms, such as cough and dyspnea, are far more likely to occur in patients with diffuse infiltrate. Uncommon sites of involvement include gastrointestinal ulcers,[27] intracerebral lesions and meningitis,[28] and skin ulcers.[26] In patients whose illness is rapidly progressive, the features of disseminated intravascular coagulation have been recognized. This latter manifestation tends to carry an extremely poor prognosis.[24]

Diagnosis

A prompt diagnosis requires a high degree of suspicion. The goal is to identify the infecting organism quickly from biologic material. The organisms may be seen circulating in peripheral blood within phagocytes. The peripheral blood smear should be diligently searched in all febrile AIDS patients.[29] When looked for, the characteristic intracellular yeast can be found in close to half the patients. In one series, 12 of 26 patients had recognizable yeasts of *H capsulatum* in peripheral blood, and in an astonishing 10 of 12, the peripheral blood film was the first hint of the fungal cause of the febrile illness.[22] The organism is readily recovered from blood cultures, especially when the lysis centrifugation technique is used. In a series from Indiana University Hospitals, the blood culture was positive in 91% of the patients whose progressive disseminated histoplasmosis complicated AIDS.[24] Even though the blood culture is frequently positive, perhaps the most rapid and sensitive test available is the examination of the bone marrow.[16,23] The organisms are readily seen in macrophages with the use of either a silver stain or by the periodic acid–Schiff stain. The advantage of the bone marrow examination is its simplicity. The diagnosis can usually be established within hours after doing a bone marrow biopsy. The organism may also be recognized in bronchoalveolar lavage (BAL) specimens[21] and in histopathologic sections prepared from biopsies of skin, lymph nodes, or other tissues.

Serologic testing is frequently extremely helpful. The immunodiffusion and complement fixation (CF) tests are frequently positive; when used together, these serologic tests will identify about 80% of involved patients.[24] The main drawbacks to the use of these serologic tests are poor sensitivity early in the illness, poor sensitivity in the most severely immunosuppressed, and a long turnaround time. The best single serologic test is measurement of the histoplasma polysaccharide antigen (HPA) level by radioimmunoassay.* In one series, the

*The test is performed by the Histoplasmosis Reference Laboratory, 1001 W 10th St, OPW441, Indianapolis, IN 46202-2879; phone 1-800-HISTO-DG.

test was positive in the urine of 70 of 72 HIV-infected patients with disseminated histoplasmosis.[30] This test is useful both for diagnosis and for monitoring treatment response and early relapse.[31] The measurement of HPA is extremely valuable in AIDS patients with this disease because the burden of organisms is so high. The test is not as useful in other forms of histoplasmosis, especially in more immunocompetent hosts.

Treatment

Similar to many other opportunistic infections complicating AIDS, progressive disseminated histoplasmosis cannot be "cured." Following the successful initial induction of treatment, lifelong suppressive therapy is needed. The incidence of relapse is unacceptably high in patients who do not receive long-term suppressive therapy. This was clearly established early during the epidemic, when upward of 50% of patients suffered a relapse after an initially successful treatment course.[26]

The mainstay of therapy for the disease in patients with AIDS is still amphotericin B. Although the exact dose required for stabilizing a patient is unknown, most agree that an initial induction course of between 500 and 1,000 mg should be given until a patient is clinically stable.[24,26] This, then, can be followed by itraconazole, 200 mg twice a day for the life of the patient.[32] Recent information shows that stable patients with progressive disseminated histoplasmosis complicating AIDS may be treated safely with itraconazole as primary therapy. These patients should receive the drug in a dose of 200 mg twice a day for life.[33] Fluconazole has also been tried for long-term maintenance, but it is not as effective as itraconazole.

Blastomycosis

Blastomycosis is an uncommon disease even in its endemic area. Blastomycosis complicating AIDS is an extremely uncommon infection, with only one large series[34] and occasional additional cases reported in the literature.

Epidemiology and Pathogenesis

Because of the small number of cases described, it is difficult to discuss the epidemiology. Whereas many cases of dual infection (HIV and blastomycosis) were reported from areas known to be endemic for the fungus, a number of patients were seen in areas normally considered outside the endemic zone.[34] Although it is possible that some patients recognized outside the endemic area were incubating their primary infection before the development of overt clinical illness, many had been away from all possible contact with the endemic area for several years. Thus, it is likely that HIV-infected patients may reactivate previously dormant foci of blastomycosis once T-cell–mediated immunity fails.

Clinical Manifestations

The spectrum of disease of blastomycosis is variable. It ranges from an indolent, slowly progressive pulmonary disease to a rapidly disseminating and fatal illness involving many organs. The lungs are usually involved. Radiographic manifestations of the disease are variable, ranging from segmental or lobar infiltrates to a large number of moderately sized pulmonary nodules. In a few patients with rapidly progressive and widely disseminated disease, the radiograph shows rapidly evolving reticulonodular infiltrates, indistinguishable from progressive disseminated histoplasmosis or *Pneumocystis carinii* pneumonia. Fulminant interstitial and miliary disease may also be seen, which has on occasion progressed to the adult respiratory disease syndrome. Central nervous system involvement is common and is usually symptomatic.[34]

Diagnosis

The standard of diagnosis is cultural recovery of the fungus from biologic material, but this is usually time-consuming. Direct visualization of the organism (a characteristic large yeast with a single broad-necked bud) from biologic material, such as BAL fluid, or histopathologic examination of biopsy material is faster. The single best test for diagnosis is the microscopic examination of respiratory specimens after 10% potassium hydroxide digestion.[3] In digested specimens, other components of the sputum are dissolved, leaving the characteristic yeast visible. Good results may also be obtained by staining respiratory specimens with the Papanicolaou stain.[35] Standard serologic tests are not considered reliable enough. When positive, they help to focus the search for *B dermatitidis*.[36] There is no commercially available skin test.

Treatment

The mainstay of the treatment of patients with blastomycosis and AIDS is still amphotericin B. The drug should be used in all patients where the pace of the disease is rapid and where there is evidence of central nervous system involvement.[34] In this subset of patients, primary therapy with azoles is inappropriate. The exact dose needed for the stabilization of a patient with blastomycosis and AIDS is not established. Most agree that as much as 2 grams of the drug should be delivered. Following clinical stabilization, the patient is then placed on a regimen of itraconazole, 200 mg twice a day, which should be maintained for the duration of the patient's life.[34,37] Although suppressive therapy with itraconazole is successful in nonmeningeal disease, it is unclear whether central nervous system blastomycosis can be successfully suppressed with oral azoles. The role of fluconazole is considered uncertain in this illness.[38]

Coccidioidomycosis

Epidemiology

Cases of coccidioidomycosis complicating AIDS have been described with increasing frequency from the endemic areas of the United States. Although this combination of infections was a latecomer to opportunistic infections complicating HIV infection, it has now

assumed increasing frequency as the epidemic has moved inland from the West Coast.[39] In the large urban centers of Arizona, for example, coccidioidomycosis is now the third most frequently reported opportunistic infection complicating AIDS.[40]

The study of coccidioidomycosis is unique among the endemic mycoses because of the performance of a carefully conducted prospective study in the Tucson-Phoenix metropolitan area. In this study, 170 HIV-infected patients were observed from the diagnosis of HIV disease. The study has shown that active coccidioidomycosis frequently develops among HIV-infected patients living in the endemic area. By the end of 3½ years of follow-up, about 25% of the patients had active disease. For most patients in whom active coccidioidomycosis developed, the disease was the result of primary infection. For at least two patients, however, the disease was due to reactivation. These two patients had a positive coccidioidin skin test on enrollment in the study, and in both, severe progressive coccidioidomycosis developed during the period of observation.[40]

Pathophysiology

From the above-mentioned large cohort study, it appears that with decreasing T-cell–mediated immunity, the risk of acquiring a progressive infection increases. The major risk for the development of progressive coccidioidomycosis was a CD4 count of less than 250×10^9 per liter. Surprisingly, the length of residency in the endemic area was not correlated with the development of active disease.[39,40]

Clinical Manifestations

The clinical manifestation of coccidioidal infection occurring among HIV-infected patients depends on a patient's CD4 count at the time of diagnosis. In patients with normal or near-normal CD4 counts, the infection resembles the disease seen in immunologically intact persons. The infection may produce single nodules, cavities, or infiltrates that are indistinguishable from those seen in normal hosts. In most of these patients, the course of the coccidioidal infection is mild.[39]

In patients with more severe immunosuppression, active coccidioidomycosis frequently occurs as a fulminant respiratory infection. Symptoms are fever, weight loss, and cough productive of mucopurulent sputum.[39,40]

Coccidioidomycotic meningitis is fairly common. In a large series reported from Phoenix, 14 of 91 patients with AIDS and coccidioidomycosis had meningitis.[41] Symptoms are variable, ranging from minimal alterations in the level of cognition to the rapid development of coma. Whereas in many patients the chest radiograph is abnormal, in some patients the sole manifestation of the infection is meningitis. In the endemic area, the diagnostic suspicion must be great to facilitate timely diagnosis. Early lumbar puncture should be considered in all patients in the high-risk group who present with even minimal alteration in cognition.

The chest radiograph is highly variable. Among patients without severe immunocompromise, the radiographic picture of coccidioidomycosis is similar to that seen in a normal host. In patients with more severely impaired immunity, the characteristic pattern is either a diffuse macronodular infiltrate or a diffuse reticulonodular infiltrate, indistinguishable from *P carinii* pneumonia or progressive disseminated histoplasmosis. Survival among patients with the severe form of pulmonary disease has been poor.[39-41]

Diagnosis

Diagnosis requires a high degree of suspicion, especially in patients coming to medical attention outside the endemic area. Physicians caring for HIV-infected patients must obtain a careful travel history so as not to miss regionally acquired diseases far removed from their endemic area. The cornerstone of diagnosis is either cultural recovery of the organism or its visualization in respiratory secretions or histopathologic specimens. Although endospores may be seen in expectorated sputum or in respiratory secretions obtained by BAL, either by the use of 10% potassium hydroxide digestion or by the Papanicolaou technique, the diagnostic sensitivity is low and is greatly dependent on the expertise of a laboratory. In a recently completed study, cytologic identification of spherules by either technique occurred in about 40% of the proven cases.[42] Cultural recovery of the organism is more common, but requires a lengthy period of incubation. Generally speaking, when the pace of the disease is rapid and simple cytologic examination is negative, one must resort to transbronchial biopsy, and should that fail, to thoracoscopic or traditional open-lung biopsy. Diagnostic bronchoscopy often reveals large endobronchial ulcers. Biopsy of these ulcers is often positive for the organism.

Serologic testing has a major role to play in the diagnosis of coccidioidomycosis. Although standard serologic tests may not be positive, they are extremely helpful when they are positive in the appropriate patients.[40] For screening, the immunodiffusion test for both immunoglobulin M and G antibodies should be used, and when positive, the CF serologic test should be obtained. This CF test is extremely helpful and should be repeated frequently during the course of a patient's illness. In addition to its diagnostic value, the CF test is helpful in monitoring the progression of the infection. Serology is the mainstay of diagnosis in suspected cases of coccidioidomycotic meningitis because cultural recovery of the fungus is unreliable. The serologic test of choice for the diagnosis of coccidioidomycotic meningitis is the cerebrospinal fluid CF test.

Treatment

All HIV-infected patients with coccidioidomycosis should be treated, and this treatment should be maintained for the patient's life. Although exact recommendations are difficult, most experts living in the endemic area recommend amphotericin B as primary therapy for patients presenting with diffuse pulmonary infiltrates.[39,41] Due to the extremely fast pace of the disease, the more

slowly acting azoles are likely to fail. Once a patient's clinical course has stabilized on a regimen of amphotericin B, it is safe to switch to fluconazole in minimum doses of 400 mg daily. There is some experience with higher doses, but as yet, there is no proof that the higher doses are more effective. In patients presenting with focal pulmonary lesions rather than the rapidly progressive diffuse pulmonary infiltrates, fluconazole may be used as primary therapy.

Ketoconazole has been used in the treatment of the various forms of coccidioidomycosis, but its effectiveness in HIV-infected patients is difficult to evaluate. Itraconazole has also been used in some patients with coccidioidomycosis and appears to be effective in carefully selected patients.

Fluconazole treatment of coccidioidal meningitis in HIV-infected patients has been reported recently. Although most patients in the study were not HIV-infected, nine of the patients were, and their response was similar to that in the larger group. In this group, the overall response rate was 79%.[43]

The question is frequently asked whether all HIV-infected patients with a positive coccidioidin or spherulin skin test should receive therapy. Largely on the basis of the cohort study from Arizona, it appears that the risk of active disease developing is low enough that treatment is not warranted until disease becomes apparent.[40] Extreme vigilance is required, however, to monitor all such patients to recognize and treat quickly reactivated disease.

REFERENCES

1. Schaffner A, Davis CE, Schaffner T, Markert M, Douglas H, Braude AI: In vitro susceptibility of fungi to killing by neutrophil granulocytes discriminates between primary pathogenicity and opportunism. J Clin Invest 1986; 78:511-524

2. Goodwin RA Jr, Des Prez RM: Histoplasmosis. Am Rev Respir Dis 1978; 117:929-956

3. Sarosi GA, Davies SF: Blastomycosis. Am Rev Respir Dis 1979; 120:911-938

4. Drutz DJ, Catanzaro A: Coccidioidomycosis (pt I). Am Rev Respir Dis 1978; 117:559-585

5. Drutz DJ, Catanzaro A: Coccidioidomycosis (pt II). Am Rev Respir Dis 1978; 117:727-771

6. Taborda A, Arechavala AI: Paracoccidioidomycosis, *In* Sarosi GA, Davies SF (Eds): Fungal Diseases of the Lung, 2nd edition. New York, NY, Raven Press, 1993, pp 85-94

7. Goodwin RA Jr, Loyd JE, Des Prez RM: Histoplasmosis in normal hosts. Medicine (Baltimore) 1981; 60:231-266

8. Sarosi GA, Davies SF: Fungal diseases, *In* Simmons DH, Tierney DF (Eds): Current Pulmonary, Vol 13. Chicago, Ill, Mosby Year Book, 1992, pp 257-287

9. Schaffner A, Douglas H, Braude A: Selective protection against conidia by mononuclear and against mycelia by polymorphonuclear phagocytes in resistance to *Aspergillus*—Observations on these two lines of defense in vivo and in vitro with human and mouse phagocytes. J Clin Invest 1982; 69:617-631

10. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA: Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984; 100:345-351

11. Pursell KJ, Telzak EE, Armstrong D: *Aspergillus* species colonization and invasive disease in patients with AIDS. Clin Infect Dis 1992; 14:141-148

12. Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA: Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324:654-662

13. Lortholary O, Meyohas MC, DuPont B, et al: Invasive aspergillosis in patients with acquired immunodeficiency syndrome: Report of 33 cases. Am J Med 1993; 95:177-187

14. Goodwin RA Jr, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM: Disseminated histoplasmosis: Clinical and pathologic correlations. Medicine (Baltimore) 1980; 59:1-33

15. Davies SF, Khan M, Sarosi GA: Disseminated histoplasmosis in immunologically suppressed patients: Occurrence in a nonendemic area. Am J Med 1978; 64:94-100

16. Davies SF, McKenna RW, Sarosi GA: Trephine biopsy of the hone marrow in disseminated histoplasmosis. Am J Med 1979; 67:617-622

17. Centers for Disease Control (CDC): Update on acquired immunodeficiency syndrome (AIDS) among patients with hemophilia A. MMWR 1981; 31:644-652

18. CDC: Revision of the CDC surveillance case definition of acquired immunodeficiency syndrome. JAMA 1987; 258:1143-1154

19. Bonner JR, Alexander WJ, Dismukes WE, et al: Disseminated histoplasmosis in patients with the acquired immune deficiency syndrome. Arch Intern Med 1984; 144:2178-2181

20. Wheat LJ, Slama TG, Zeckel MS: Histoplasmosis in the acquired immunodeficiency syndrome. Am J Med 1985; 78:203-210

21. Salzman SH, Smith RL, Aranda CP: Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a nonendemic setting. Chest 1988; 93:916-921

22. Nightingale SD, Parks JM, Pounders SM, Burns DK, Reynolds J, Hernandez JA: Disseminated histoplasmosis in patients with AIDS. South Med J 1990; 83:624-630

23. Johnson PC, Khardori N, Najjar AF, Butt F, Mansell PW, Sarosi GA: Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1988; 85:152-158

24. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al: Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. Medicine (Baltimore) 1990; 69:361-374

25. Dismukes WE: Cryptococcal meningitis in patients with AIDS. J Infect Dis 1988; 157:624-628

26. Sarosi GA, Johnson PC: Disseminated histoplasmosis in patients infected with human immunodeficiency virus. Clin Infect Dis 1992; 14(suppl):60-67

27. Haggerty CM, Britton MC, Dorman JM, Marzoni FA Jr: Gastrointestinal histoplasmosis in suspected acquired immunodeficiency syndrome. West J Med 1985; 143:244-246

28. Anaissie E, Fainstein V, Samo T, Bodey GP, Sarosi GA: Central nervous system histoplasmosis—An unappreciated complication of the acquired immunodeficiency syndrome. Am J Med 1988; 84:215-217

29. Henochowicz S, Sahovic E, Pistole M, Rodrigues M, Macher A: Histoplasmosis diagnosed on peripheral blood smear from a patient with AIDS. JAMA 1985; 253:3148

30. Wheat LJ, Connolly-Stringfield P, Kohler RB, Frame PT, Gupta MR: *Histoplasma capsulatum* polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1989; 87:396-400

31. Wheat LJ, Connolly-Stringfield P, Blair R, Connolly K, Garringer T, Katz B: Histoplasmosis relapse in patients with AIDS: Detection using *Histoplasma capsulatum* variety *capsulatum* antigen levels. Ann Intern Med 1991; 115:936-941

32. Wheat J, Hafner R, Wulfsohn M, et al: Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome—The National Institute of Allergy and Infectious Diseases Clinical Trials and Mycoses Study Group Collaborators. Ann Intern Med 1993; 118:610-616

33. Wheat LJ, Hafner RE, Korzun AH, et al: Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Med 1995; 98:336-342

34. Pappas PG, Pottage JC, Powderly WG, et al: Blastomycosis in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1992; 116: 847-853

35. Sanders JS, Sarosi GA, Nollet DJ, et al: Exfoliative cytology in the rapid diagnosis of pulmonary blastomycosis. Chest 1977; 72:193-196

36. Davies SF: Serodiagnosis of histoplasmosis. Semin Respir Infect 1986; 1:9-15

37. Sarosi GA, Davies SF: Therapy for fungal infections. Mayo Clin Proc 1994: 69:1111-1117

38. Como JA, Dismukes WE: Oral azole drugs as systemic antifungal therapy. N Engl J Med 1994; 330:263-272

39. Fish DG, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during human immunodeficiency virus infection—A review of 77 patients. Medicine (Baltimore) 1990; 69:384-391

40. Ampel NM, Dols CL, Galgiani JN: Coccidioidomycosis during human immunodeficiency virus infection: Results of a prospective study in a coccidioidal endemic area. Am J Med 1993; 94:235-240

41. Singh VR, Smith DK, Sarosi GA, et al: Coccidioidomycosis in HIV Infected Patients: Review of 83 Cases—Abstracts of the 1993 Infectious Diseases Society of America (IDSA) Annual Meeting. Clin Infect Dis 1993; 17:543, abstract No. 74

42. DiTomasso JP, Ampel NM, Sobonya RE, Bloom JW: Bronchoscopic diagnosis of pulmonary coccidioidomycosis: Comparison of cytology, culture and transbronchial biopsy. Diagn Microbiol Infect Dis; in press

43. Galgiani JN, Catanzaro A, Cloud GA, et al: Fluconazole therapy for coccidioidal meningitis. Ann Intern Med 1993; 119:28-35

Epitomes

Important Advances in Clinical Medicine

Urology

Ira D. Sharlip, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under the direction of Ira D. Sharlip, MD, and the panel.

Laser Treatment of Genital Condylomata Acuminata

GENITAL CONDYLOMATA are caused by the human papillomavirus (HPV), a heterogeneous family of at least 34 distinct types of viruses. Condylomata, caused by HPV types 16, 18, and 31, have been associated with cervical cancer in women and penile carcinoma in men. Genital infections in humans may present in two structural forms: as a classical verrucous papillary growth that may range from 1 mm to several centimeters in diameter, or as a flat plaque that is not visible to the naked eye. Women may have lesions on the cervix, introitus, perineum, and perianal region. In men, the lesions may occur on the penile shaft, scrotum, and perianal region. These lesions are best identified by magnified penile surface scanning after applying a 5% solution of acetic acid to the genitals and identifying white plaques ("acetowhite") that are known to indicate infection with HPV. Urethroscopy is indicated when patients have lesions on the glans or at the meatus.

Treatment modalities include the application of a topical antimetabolite such as fluorouracil or podophyllum resin, cryotherapy, surgical excision, electrocautery, and laser phototherapy. The carbon dioxide and the neodymium:yttrium-aluminum-garnet lasers are both used for the treatment of genital condylomata. More than 90% of the patients are treated under local anesthesia as outpatients.

All patients are reexamined at two months, and any residual lesions are retreated. Patients with lesions on the penile shaft are advised to use condoms for three months. The recurrence rates for laser therapy vary from 20% to 50% and are about 30% less than recurrence rates of other treatment modalities.

Laser phototherapy for genital condylomata is a rapid and effective mode of treatment and can be done on an outpatient basis. The amount of discomfort after treatment is the same as with other methods of therapy.

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REFERENCES

Kaplinsky RS, Pranikoff K, Chasan S, DeBerry JL: Indications for urethroscopy in male patients with penile condylomata. J Urol 1995; 153:1120-1121

Kling AR: Genital warts. Semin Dermatol 1992; 11:247-255

Maymon R, Shulmon A, Maymon B, et al: Penile condylomata: A gynecological epidemic disease: A review of the current approach and management aspects. Obstet Gynecol Surv 1994; 49:790-800

Stone KM: Human papilloma virus infections and genital warts: Update on epidemiology and treatment. Clin Infect Dis 1995; 1:91-97

Townsend DE, Smith LH, Kinney WK: Condylomata acuminata—Role of different techniques of vaporization. J Reprod Med 1993; 38:362-364

Should We and Can We Cure Prostate Cancer?

RANDOMIZED, CONTROLLED TRIALS are now underway that will assess the influence of prostate cancer screening on cancer-related mortality and the outcomes of radical prostatectomy versus observation with delayed androgen deprivation. Results are expected to be available within 15 years. In the interim, millions of men will have to decide whether or not to undergo diagnosis and treatment of prostate cancer, which is the second leading cause of cancer deaths in men in the United States and now kills 40,000 annually.

Increasing information about the use of serum prostate-specific antigen (PSA) levels has been essential to understanding many aspects of prostate cancer. There has been concern that PSA testing might discover the minute and clinically unimportant prostate cancer often found in autopsy series of men older than 50 and lead to unnecessary treatment. As many as 99% of tumors detected by elevated PSA levels (>4 ng per ml) or a digital rectal examination, however, have the volume or grade of clinically important cancer. When the PSA test is combined with rectal examination, two thirds of newly diagnosed cases are found when they are still localized, whereas only a third were localized when found before using the PSA test. A single elevated PSA level has been shown to have a sensitivity of 73% for detecting prostate

cancer in the succeeding four years and a specificity of 91%.

Prostate-specific antigen is present in the serum in both free and protein-bound forms. For still obscure reasons, benign glandular hyperplasia appears to produce a proportionally greater amount of the free form, and adenocarcinoma appears to produce more of the protein-bound form. This difference has been exploited recently to improve PSA specificity. Within the total PSA range of 4 to 10 ng per ml, which characterizes most curable cancers, the measurement of the ratio of free to total PSA, with a cutoff of 24% of total PSA or lower warranting biopsy, promises to maintain the same sensitivity while improving the positive predictive value. It should also eliminate the 31% incidence of negative biopsies in men with an elevated PSA level due to prostatic hyperplasia. With total PSA levels of greater than 10 ng per ml, the risk of prostate cancer is so high (and proportionally less curable) that measurement of the free fraction adds little to the decision about prostate biopsy.

The natural history of prostate cancer is now better documented. Serial PSA measurements demonstrate that untreated prostate cancer is only infrequently latent and is progressive in 87%, albeit with a generally slow growth rate. Studies have shown that ten years after diagnosis, 42% of men with initially localized medium-grade and 74% of those with high-grade cancer have bony metastases. Beyond ten years, prostate cancer is the cause of death even in 56% of palliatively treated men who initially had only low-stage, low-grade cancer. The estimated years of life expectancy lost by men aged 65 to 75 with localized prostate cancer who are treated conservatively is as long as five years with medium-grade and as long as eight years with high-grade cancer.

In contrast, men with clinically organ-confined prostate cancer who undergo radical prostatectomy have a 79% undetectable PSA rate at a mean three-year follow-up. The actuarial progression-free survival rate with undetectable PSA levels at five years is 75%. Even with high-grade cancer, 43% of those without lymph node metastases who undergo radical prostatectomy have undetectable PSA at five years. These men are apparently cured because surgical failure is almost always manifested by detectable PSA within five years if it is not obscured by adjuvant androgen-deprivation therapy. The reappearance of detectable PSA more than five years after surgical treatment is rare. Those with detectable postoperative PSA appear to be subject to the natural history previously described.

The use of undetectable PSA after five years as a marker for surgical cure eliminates concerns about length- and lead-time bias inherent in outcomes assessed by the time to clinical progression or death. Because of the generally slow growth rate of localized prostate cancer, currently reported cancer-related mortality rates are a reflection of treatment decisions and interventions from more than a decade ago. They do not yet reflect the expected effect, as modern radical prostatectomy and PSA screening have been widely used for less than a decade.

Modern radical prostatectomy has low morbidity and mortality. The contemporary operative mortality is less than 1%. Many experienced urologists are reporting continence rates of 95% and potency preservation rates of 70% in selected men with good preoperative potency in whom nerve sparing was thought unlikely to compromise tumor-free margins. Median total hospital stays of three days are increasingly reported.

At this time, the best available data indicate that curative treatment of prostate cancer is both necessary and possible in appropriately selected men. Among those with clinically organ-confined prostate cancer who are likely to be at risk for at least ten years, as many as 75% undergoing radical prostatectomy are apparently cured and not subject to the ominous future they would otherwise face.

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REFERENCES

Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J: Long-term survival among men with conservatively treated localized prostate cancer. JAMA 1995; 274:626-631

Aus G, Hugosson J, Norlen L: Long-term survival and mortality in prostate cancer treated with noncurative intent. J Urol 1995; 154:460-465

Catalona WJ, Smith DS, Wolfert RL, et al: Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA 1995; 274:1214-1220

Gann PH, Hennekens CH, Stampfer MJ: A prospective evaluation of plasma prostate-specific antigen for detection of prostate cancer. JAMA 1995; 273: 289-294

Laparoscopic Burch Bladder Neck Suspension

LAPAROSCOPIC SURGICAL TECHNIQUES are still evolving in the field of urology. Some procedures have gained wide acceptance (such as laparoscopic lymphadenectomy), whereas others still remain cloaked in controversy (laparoscopic nephrectomy and varicocelectomy). A new urologic laparoscopic procedure that is rapidly gaining acceptance is the laparoscopic Burch bladder neck suspension.

Laparoscopic Burch bladder neck suspension was originally performed as an intraperitoneal procedure that in fact added to morbidity. The surgical approach to the bladder neck area has now moved to an extraperitoneal approach. Surgical treatment is easier, morbidity has decreased, and the procedure is now done on an outpatient basis. The Foley catheter can also be removed the next day in almost all patients with successful voiding. Blood loss has been negligible. Patients are generally able to return to work, without heavy lifting, seven to ten days after the procedure. A disadvantage of this procedure is the occasional mistaken placement of sutures or staples in the bladder. This can happen during open or needle suspension procedures, and patients need to be cystoscoped at the time of the operation to avoid this complication or to remove the sutures or staples. Another possible disadvantage of this procedure is the short-term follow-up time in published series.

Another criticism of this procedure has been the operative time. As surgeons' experience increases, this proce-

dure can generally be completed in 75 to 90 minutes. Another problem with this procedure is that it is not indicated for type III urinary incontinence. If a patient has an associated disorder such as an enterocele or rectocele that requires repair, this would have to be approached vaginally at the same time.

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REFERENCES

McDougall EM, Klutke D, Cornell T: Two-Year Follow-up Comparison of the Transvaginal (VBNS) and the Laparoscopic (LBNS) Bladder Neck Suspension for Anatomic Stress Urinary Incontinence. Proceedings of the American Urological Association 1995; 153:3.56 (abstract #510)

Shanberg A, Green PT, Chamberlin D: Laparoscopic Mesh Bladder Neck Suspension—Three-Year Follow-up. To be presented at the American Urological Association meeting, Orlando, Florida, May 1996

Laparoscopic Orchiopexy for Intraperitoneal Testicles

THE DIAGNOSTIC BENEFITS of laparoscopy in the evaluation of nonpalpable testicles in children have been well established. Laparoscopy has been shown to be superior to other diagnostic modalities such as computed tomographic scanning, magnetic resonance imaging, or ultrasonography.

In the past two years, techniques have been described that attempt to salvage intra-abdominal testicles with two-stage Fowler-Stephens procedures. If this is done laparoscopically, the spermatic cord is either clipped or treated with laser to allow the testicle to develop a collateral blood supply through the artery to the vas deferens. Three months later, the child is usually reexplored, and the spermatic vessels are cut to allow for additional length in bringing the testicle down into the scrotum.

We currently have used this technique in 15 children with intra-abdominal testes and have been successful in bringing the testicle into the scrotum in all but one child. That child underwent a two-stage Fowler-Stephens procedure.

These are two new interesting and exciting uses of laparoscopy in urology that have improved present-day surgical techniques.

Within the past year, several techniques have now become available where these intra-abdominal testicles can be dissected free of attachments laparoscopically and brought into the scrotum in a one-stage outpatient procedure.

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REFERENCES

Gill IS, Clayman RV, McDougall E: Advances in urological laparoscopy. J Urol 1995; 154:1275-1294

Poppas DP, Lemack GE, Mininberg DT: Laparoscopic orchiopexy: Clinical experience and description of technique. J Urol 1996; 155:108-111

Managing Ureteral Calculi

UROLOGISTS HAVE numerous treatment options to choose from when managing patients with ureteral calculi. Stone location and size are the most critical factors in selecting treatment. Therapeutic options can be divided into conservative observation and minimally invasive and invasive techniques.

Most ureteral stones pass spontaneously. Symptomatic stones can be observed if there is no infection or high-grade ureteral obstruction and when pain and nausea or vomiting are tolerable. Stones less than 4 mm in size have a 57% spontaneous passage rate, but only 8% of stones greater than 6 mm in diameter pass uneventfully. A complication rate of 20% was identified during endoscopic extraction in patients with symptoms lasting longer than four weeks in comparison with a 7% complication rate when symptoms lasted less than four weeks. This study suggests that a patient with a ureteral calculus of less than 4 mm may be observed safely for four weeks while awaiting spontaneous passage. Patients with a stone greater than 6 mm in diameter or with a stone of any size and symptomatic for longer than four weeks may not benefit from waiting for spontaneous passage.

An indwelling double J ureteral stent has been used to assist in the passage of ureteral calculi. This is most beneficial for small distal ureteral calculi. Passive ureteral dilatation and decompression of a dilated proximal ureter, thus allowing coaptation of the ureteral walls, are the likely modes of success for stent-assisted stone passage.

Extracorporeal shock-wave lithotripsy (ESWL) is effective in fragmenting urinary calculi. It is most effective for renal calculi and upper and distal ureteral stones. Stones in the upper ureter (superior to the sacroiliac joint as seen on an abdominal radiograph) are best treated initially with ESWL. Stone-free rates differ depending on a urologist's experience and lithotriptor but generally range from 60% to 88% for upper and midureteral stones and from 79% to 91% for distal ureteral stones.

Controversy in the management of distal ureteral calculi remains divided between in situ ESWL versus ureteroscopic stone extraction. In situ ESWL is attractive because no instrumentation is required and minimal operator skill is necessary. Drawbacks include difficulties in targeting radiolucent calculi and the inability to determine ease of fragmentation preoperatively. Retreatment rates relative to ureteroscopy are higher, and the time to complete stone passage may require weeks. Machine availability can be a limiting factor. The effect of shock waves on ovarian function remains unknown, so the treatment of fertile women should be approached with caution. The ureteroscopic treatment of distal ureteral calculi is effective because of its high success rate, 93% versus 83%, its minimal short- and long-term complications, and minimal associated ancillary procedures compared with ESWL. It also remains a fall-back procedure when ESWL fails. The complications of ureteroscopy include ureteral or bladder hemorrhage, infection, ureteral perforation, and the small chance of ureteral stricture. Future emphasis for the primary treatment of distal ureteral stones may be based on the cost differential between these two procedures.

Rigid and flexible ureteroscopes have been miniaturized, easing placement and decreasing trauma to the

ureter. The entire collecting system can be visualized so that ureteroscopy may be used for both the diagnosis and treatment of urinary stones. Intracorporeal lithotripsy equipment has been miniaturized for routine use through small ureteroscopes when basket extraction for removing calculi in toto are unsuccessful. Electrohydraulic, ultrasonic, and laser lithotripsy are the primary techniques used today. Each modality has distinct advantages and disadvantages, and their use is primarily dependent on the surgeons' needs and experience.

Open ureterolithotomy is regarded as the final line of treatment for previously failed, minimally invasive therapy, usually for long-standing large upper ureteral stones. Open surgical approaches include access through a dorsal lumbotomy, flank, midline, and Gibson incisions. Laparoscopic ureterolithotomy, first described in 1979, is an alternative to open ureterolithotomy. Transperitoneal and retroperitoneal laparoscopic approaches have been described. The procedure may require conversion to an open surgical procedure in as many as 15% of cases.

The optimal treatment of ureteral calculi depends on numerous factors, including stone size, type, and location. Patients' preference, equipment availability, and surgeons' experience will dictate optimal management.

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REFERENCES

Francesca F, Grasso M, Lucchelli M, et al: Cost-efficacy comparison of extracorporeal shock wave lithotripsy and endoscopic laser lithotripsy in distal ureteral stones. J Endourol 1993; 7:289-291

Hubner MA, Irby P, Stoller ML: Natural history and current concepts for the treatment of small ureteral calculi. Eur Urol 1993; 24:172-176

Leventhal EK, Rozanski TA, Crain TW, Deshon GE Jr: Indwelling ureteral stents as definitive therapy for distal ureteral calculi. J Urol 1995; 153:34-36

Surgical Treatment of Peyronie's Disease

PEYRONIE'S DISEASE was first described by Francois Gigot de la Peyronie in 1743 as a fibrous thickening of the penile shaft associated with pain and curvature. Peyronie's disease can affect as much as 1% of the generally active male population, with a peak incidence between 45 and 60 years of age. A Peyronie's plaque is characterized by a fibrous scar in the tunica albuginea of the corpus cavernosum that restricts the elasticity of the penis and causes abnormal curvature on erection. The goal of the surgical treatment of Peyronie's disease is to straighten the penis, allowing the resumption of intercourse. The surgical correction of Peyronie's disease is not indicated for the resolution of pain, which is treated by oral pain medication or anti-inflammatory drugs. Moreover, patients are counseled not to expect lessening of penile rigidity. A vascular evaluation with duplex ultrasonography before and after intracavernosal administration of prostaglandin (PGE_1) is done on all candidates before any operation involving dissection of the neurovascular bundle to assess collateral arterial blood flow. The interruption of communications between the cavernous and dorsal arteries may result in impotence in patients with borderline erectile function.

The tunica albuginea can be plicated in patients with normal erections or in impotent patients with a good erectile response to the administration of PGE_1. In patients with dorsal curvature, deep, parallel, plicating, nonabsorbable sutures (usually 2 to 3 pairs) are placed onto the tunica albuginea at the center of the curvature 2 to 3 mm from the spongiosum on both sides. Plication is a relatively simple procedure, lasting about 30 minutes, that can be done under local anesthesia on an outpatient basis. Candidates for penile plication, however, must be informed that their penile length may decrease by 2 to 3 cm as a result of the plication. Patients are instructed to abstain from sexual intercourse for four to six weeks.

There have been many reports in the literature regarding the excision of Peyronie's plaques and placement of an autologous graft—whether dermis, dura mater, temporalis fascia, or tunica vaginalis. Inert substances, such as Dacron (Gore-Tex) or Dexon mesh, have also been used. Plaque excision, however, may result in excessive reaction and weakening of the tunica and impotence, and studies in animals have shown that the venous graft is an excellent substitute for tunica albuginea.

Therefore, in those patients with severe curvature of the penis resulting in a shortened penis, a plaque incision can be done with the use of either a dorsal vein graft, a lower saphenous vein graft, or a combination of both. The lowest portion of the saphenous vein has been used because of its few branches and the minimal dissection involved in its isolation.

Patients are discharged the following day with instructions to change the dressing once a day for ten days and to abstain from sexual intercourse for six weeks. In patients with both Peyronie's disease and severe impotence not responding to intracavernous PGE_1 administration or to a vacuum erectile device, a penile prosthesis is recommended (inflatable or semirigid).

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REFERENCES

Brock G, Nunes L, von Heyden B, Martinez-Piñeiro L, Hsu GL, Lue TF: Can a venous patch graft be a substitute for the tunica albuginea of the penis? J Urol 1993; 150:1306-1309

Ganabathi K, Dmochowski R, Zimmern P, et al: Peyronie's disease: Surgical treatment based on penile rigidity. J Urol 1995; 153:662-666

Helal MA, Lockhart JL, Sanford E, Persky L: Tunica vaginalis flap for the management of disabling Peyronie's disease: Surgical technique, results, and complications. Urology 1995; 46:390-392

Ralph DJ, al-Akraa M, Pryor JP: The Nesbit operation for Peyronie's disease: 16-year experience. J Urol 1995; 154:1362-1363

Serologic Markers in Prostate Cancer

THE PRIMARY TUMOR MARKER currently used in the diagnosis and management of prostate cancer is prostate-specific antigen (PSA). Prostate-specific antigen is produced exclusively by prostate epithelial cells and is usually de-

tected at low concentrations in the systemic circulation. Although specific to the prostate gland, PSA is not specific for prostate cancer. Benign prostatic hypertrophy (BPH), infection, instrumentation, and prostatic infarction are all known to elevate serum PSA levels in the absence of prostate cancer. As a screening test for cancer, the sensitivity of PSA is about 70%, with a specificity between 60% and 90%. Although critics question the use of a test that generates such a large number of negative biopsies, it has been shown from studies of patients having radical prostatectomy that periodic evaluation with a digital rectal examination and PSA test increases the proportion of pathologically organ-confined and potentially curable tumors from 45% to 75%.

The reference range for serum PSA levels is 0.0 to 4.0 ng per ml. Age-specific PSA reference ranges have been proposed to allow for the increase in prostatic size due to BPH as men age: 40 to 49 years, 0.0 to 2.5 ng per ml; 50 to 59 years, 0.0 to 3.5 ng per ml; 60 to 69 years, 0.0 to 4.5 ng per ml; and 70 to 79 years, 0.0 to 6.5 ng per ml. The rationale for age-specific reference ranges is that sensitivity in the younger age group (<60 years) would be increased. In older patients, the specificity of the test would be greater. A criticism of age-specific reference ranges is that the clinical course of tumors detected by mild PSA elevations (4.0 to 6.5 ng per ml) is not known. These tumors may indeed be clinically important in older men. It has been shown that an increase in the PSA level of greater than 0.75 ng per ml per year—based on at least 3 consecutive PSA levels over a 2-year period—is inconsistent with BPH and suspicious for prostate cancer. Another technique to possibly improve the specificity of PSA is to determine the ratio of free to protein-bound serum PSA. A higher proportion of PSA from patients with prostate cancer is protein bound as compared with that from patients with only BPH.

Although it is not proved that using PSA levels in cancer detection improves survival, it is well documented that the PSA test is an effective tool in staging and monitoring patients with known prostate cancer. In patients with untreated prostate cancer who are asymptomatic, the probability of having a positive bone scan with a PSA level of less than 10 ng per ml is less than 1.5% ($P < .0001$). It is now common practice to omit staging bone scans in asymptomatic, previously untreated patients with well- or moderately differentiated cancer who have a PSA level of 10 ng per ml or less.

The most clearly defined role of PSA is in monitoring patients after definitive therapy. In radical prostatectomy, the entire prostate gland is removed, and therefore, serum PSA levels should become undetectable. Detectable PSA following radical prostatectomy indicates residual disease. Following definitive radiation therapy, the serum PSA concentration should reach a nadir and remain stable. The nadir reference range after definitive irradiation is not known; in general, however, the lower the nadir value, the better the prognosis. The PSA level will ideally reach a nadir of 1.0 ng per ml or less. A progressive increase in serum PSA levels after a nadir is consistent with persistent tumor. The PSA test is less reliable for observing patients treated with androgen-deprivation (hormonal) therapy. Basic science studies have shown that expression of the PSA gene is modulated by androgens. Clinically, patients treated with androgen-deprivation therapy may have disease progression without an increase in their serum PSA level. As such, these patients should periodically have a physical examination, an assessment of symptoms of bony pain, and a serum PSA test. The PSA level is still the best tumor marker to observe patients on androgen-deprivation therapy because a rise in the level indicates disease progression and usually precedes symptoms of tumor growth.

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REFERENCES

Ruckle HC, Klee GG, Oesterling JE: Prostate-specific antigen: Critical issues for the practicing physician. Mayo Clinic Proc 1994; 69:59-68

Ruckle HC, Oesterling JE: Prostate-specific antigen and androgen deprivation therapy. World J Urol 1993; 11:227

New Options for Managing Severe Oligospermia and Azoospermia

UROLOGISTS APPROACH the management of male infertility by first trying to identify disease that may be corrected. The treatment of conditions such as varicocele, secondary hypogonadism, and obstruction may result in either or both improved sperm counts and motility and pregnancy. If correctable conditions are not present, the management of male infertility is dependent on making optimal use of the sperm that are available. Optimal use of these sperm usually requires in vitro fertilization (IVF).

Recent advances in the field of IVF have revolutionized the management of infertility due to severe oligospermia and azoospermia. The newest modification of IVF, called intracytoplasmic sperm injection (ICSI), is responsible for this change. This procedure involves injecting one sperm into each egg that is obtained from the female partner. With ICSI, the number of sperm used is the same as the number of available viable eggs, which is usually 5 to 20. This technique makes it possible for men who have nearly zero sperm counts to impregnate their partners.

If any motile sperm at all are present in the ejaculate, ICSI may be attempted. If no sperm are present in the ejaculate, pregnancy may still be achieved by the use of this procedure in some couples. Sperm may be aspirated directly from the testes if at least some spermatogenesis is found in patients with nonobstructive azoospermia. In obstructive types, spermatogenesis is usually normal, and sperm may be aspirated from any site proximal to a blockage. These sites include the testes, epididymides, vasa deferentia, and seminal vesicles.

Although few sperm can be harvested from these sites, intracytoplasmic administration of sperm removed from

the male reproductive system produces fertilization in more than half of oocytes treated and in more than three fourths of cycles initiated. Pregnancy or live births have been reported in 11% to 57% of sperm retrieval–ICSI cycles, but average about 25% per cycle in most reproductive centers. The success of ICSI is strongly influenced by the age of the female partner. Pregnancy rates in women older than 38 are notably lower than in younger women independent of the age of their male partners.

Retrieving Sperm From the Testes

Sperm may be obtained from the testes by open biopsy, needle biopsy, or by needle aspiration. Open surgical biopsy using local anesthesia is the standard technique for obtaining testicular tissue.

Needle biopsy or aspiration is simpler and easier than open biopsy for both surgeons and patients, but needle techniques provide less tissue for a gamete laboratory technician's use. The choice of needle biopsy versus open technique depends primarily on the ability of the gamete laboratory to separate minute numbers of mature spermatozoa from the testicular tissue.

Regardless of the technique used to obtain the specimen or to separate the sperm, few sperm are retrieved, and the sperm motility is very low or zero. Nevertheless, testicular sperm used for ICSI are currently producing per-cycle pregnancy rates that are only slightly less than per-cycle pregnancy rates of sperm from other sources.

Retrieving Sperm From the Epididymides

A far greater number of sperm are available from the epididymides of men with obstructive azoospermia. The two most common clinical conditions requiring epididymal sperm aspiration are congenital absence of the vasa deferentia and failed vasectomy reversal. Epididymal sperm aspiration may be done using a microsurgical or percutaneous needle technique. The motility of epididymal sperm is usually 10% to 20%.

Microsurgical epididymal sperm aspiration produces absolute numbers of motile sperm in the range of 10,000 to 1 million. If ICSI is used rather than standard IVF, sufficient sperm remain after injecting the sperm for freezing as well. With percutaneous aspiration, the volume of fluid and the total number of motile sperm are about a tenth of those that are obtained by microsurgical aspiration. With percutaneous epididymal sperm aspiration, there often are not sufficient sperm after ICSI for freezing. Percutaneous epididymal sperm aspiration is successful in obtaining sperm in two thirds to three fourths of attempts. Because the percutaneous needle technique sometimes fails to produce sperm, donor sperm or the microsurgical technique should be available as backup.

Retrieving Sperm From the Vasa and the Seminal Vesicles

When obstructive azoospermia is caused by ejaculatory duct disease, or when ejaculation is absent in conditions such as spinal cord injury, sperm are present in the vasa deferentia, provided that secondary epididymal obstruction has not occurred. It is possible to collect these sperm through a vasotomy incision. If motility is present, the chance for fertilization is good.

When ejaculatory duct obstruction has produced dilation of the seminal vesicles, or when a dilated retroprostatic or retrovesical cyst contains motile sperm, these structures may be aspirated transperineally or transrectally. Motile sperm obtained from the distal reproductive system have a good chance to achieve fertilization through ICSI.

Sperm Retrieval With Intracytoplasmic Sperm Injection Versus Surgical Reconstruction With Sperm Freezing

Sperm retrieval with ICSI is inappropriate as the first line of management for men with surgically reparable obstructive azoospermia, such as those who wish to reestablish fertility after a previous vasectomy and those who have epididymal obstruction. Birth rates following vasectomy reversal are 50% to 60%, and birth rates following vasoepididymostomy for epididymal obstruction are 40%. These rates are higher than those for a single cycle of sperm retrieval with ICSI in most reproductive centers. The current cost of a single cycle of this procedure is at least double the cost of vasectomy reversal or surgical reconstruction of the epididymis by vasoepididymostomy. In addition, the results of ICSI with frozen-thawed sperm of any origin have been reported to be as good as the results of ICSI with fresh epididymal or testicular sperm.

Therefore, a more logical choice for patients requesting vasectomy reversal after a long obstructive interval (>15 years) or for patients requesting surgical reconstruction of the epididymis is surgical treatment with simultaneous microsurgical epididymal sperm aspiration. The aspirated sperm may then be frozen and used for a subsequent ICSI if the patient remains azoospermic postoperatively. This approach is more successful and less expensive than sperm retrieval with ICSI. If the obstructive interval following vasectomy is less than 15 years, vasectomy reversal with or without microsurgical epididymal sperm aspiration is clearly preferable to any technique of sperm aspiration and ICSI.

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REFERENCES

DeVreoy P, Lin J, Goosens A, et al: Pregnancies after testicular sperm extraction and intracytoplasmic sperm injection in nonobstructive azoospermia. Hum Reprod 1995; 10:1457-1460

Nagy ZP, Verheyen G, Lin J, et al: Results of 55 intracytoplasmic sperm injection cycles in the treatment of male-immunological infertility. Hum Reprod 1995; 10:1775-1780

Schlegel PN, Palermo GD, Alikani M, et al: Micropuncture retrieval of epididymal sperm with in vitro fertilization: Importance of in vitro micromanipulation techniques. Urology 1995; 46:238-241

Sherins RJ, Thorsall LP, Dorfmann A, et al: Intracytoplasmic sperm injection facilitates fertilization even in the most severe forms of male infertility: Pregnancy outcome correlates with maternal age and number of eggs available. Fertil Steril 1995; 64:369-375

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Alerts, Notices, and Case Reports

Retrospective Diagnosis of a Fatal Case of the Hantavirus Pulmonary Syndrome, 1980

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In May 1993, an outbreak of an acute illness characterized by a prodrome of fever and variable respiratory symptoms, followed by a rapid progression to respiratory failure, was identified in young adults of the southwestern United States.[1] Initial and subsequent laboratory evidence linked this disease to a previously unrecognized hantavirus, *Sin Nombre* virus.[2,3] Although the initial cases occurred in the Four Corners region of the Southwest, cases have been identified in residents of other parts of the country, demonstrating a wider distribution of the hantavirus pulmonary syndrome (HPS) than was initially thought.[4,5] Definite cases have been retrospectively identified from 1978, the 1980s, and the early 1990s (S.R.Z., unpublished data), suggesting that this virus was present before the 1993 outbreak.[6-8]

The uniqueness and severity of this outbreak resulted in widespread publicity and numerous reports in the scientific literature and in the general press.[1-4] After reading several general articles on the hantavirus outbreak, a resident of San Francisco, California, noticed that the illness was similar to that of her son who had died of the adult respiratory distress syndrome in 1980 after returning to California from New Mexico. She requested that an investigation be undertaken to determine if her son had died of HPS.

Report of a Case

The patient was a 22-year-old, previously healthy man in whom fever, chills, myalgias, headache, and weakness developed four days before his admission. The day before admission, the patient had nausea, vomiting, diarrhea, and dyspnea. On the morning of February 28, 1980, he was examined in a San Francisco hospital outpatient clinic, diagnosed with an acute viral syndrome, and sent home with recommendations for supportive care. He returned to the hospital later that evening with progressive dyspnea and weakness and was admitted with a diagnosis of the adult respiratory distress syndrome.

The patient arrived in California in February 1980 about ten days before the onset of his illness after he had taken three to six weeks to hitchhike from New Mexico. In the six months before leaving New Mexico, the patient lived alone in an adobe brick house in Lama, New Mexico. His father, who had been living in an adjacent dwelling at the time, reported that rodents and their excreta had been seen in and near the house. The patient often hunted rabbits and squirrels in the surrounding woods, but was not involved in trapping rodents. He hauled previously gathered wood on a daily basis from a wood pile located near his home. During his last month in New Mexico, he built a wooden porch onto his home.

On hospital admission, the patient was noted to be alert and in obvious respiratory distress. His temperature was 39.4°C (103°F), his heart rate was 130 beats per minute and weak, his systolic blood pressure was 68 mm of mercury, and his diastolic blood pressure was not obtainable. He had perioral cyanosis, and his extremities were cyanotic and mottled. Chest examination revealed coarse rales and rhonchi on the right side.

The peripheral leukocyte count was 23.2×10^9 per liter (23,200 per mm^3) with 0.59 (59%) segmented neutrophils, 0.37 (37%) band forms, and 0.04 (4%) lymphocytes; the hematocrit was 0.70 (70%), and the platelet count was 55×10^9 per liter (55,000 per mm^3). The serum creatinine level was 160 μmol per liter (1.8 mg per dl). The patient's oxygen saturation was 52 mm of mercury, his bicarbonate concentration was 16 mmol per liter, and his pH was 7.42 while he was breathing room air. The prothrombin time was 25.8 seconds, and the activated partial thromboplastin time was 77.8 seconds. Urinalysis revealed 1+ protein and trace hemoglobin. A chest radiograph revealed bilateral interstitial infiltrates.

An endotracheal tube was inserted, and the patient was given parenteral streptomycin and ampicillin and admitted to the intensive care unit. Respiratory arrest occurred a few minutes after his arrival at the intensive care unit. Throughout the hour-long effort to resuscitate the patient, large amounts of frothy white fluid were obtained from the endotracheal tube. The patient was unable to be resuscitated and died shortly thereafter of cardiac arrest.

Routine blood and tissue cultures were negative for viral, bacterial, and fungal pathogens. An autopsy revealed severe pulmonary edema with serosanguinous pleural, pericardial, and peritoneal effusions, hepatosplenomegaly, and cardiac hypertrophy and patchy fibrosis. The cause of death, as reported on the death certificate, was the adult respiratory distress syndrome of unknown cause.

In December 1993, histopathologic examination of archival autopsy tissues was done at the Centers for

(Schwarcz SK, Shefer AM, Zaki SR: Retrospective diagnosis of a fatal case of the hantavirus pulmonary syndrome, 1980. West J Med 1996; 164:348-350)

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Disease Control and Prevention. The main histopathologic features were found in the lungs, which showed moderate interstitial pneumonitis with congestion, edema, and mononuclear cell infiltration. The cellular infiltrate was composed of mixtures of lymphocytes, monocytes, and enlarged cells with the appearance of immunoblasts. Extensive amounts of intra-alveolar edema fluid and fibrin, along with focal hemorrhages, were seen. Focal hyaline membranes were also noted. Immunoblasts similar to those seen in the lung were also seen in the red pulp and the periarteriolar sheath of the spleen as well as in the portal triads.

Hantaviral infection was confirmed through immunohistochemical staining of multiple tissues using a monoclonal antibody that cross-reacts with conserved hantaviral nucleocapsid epitopes as well as *Sin Nombre* virus-specific polyclonal serum.[9] Pathognomonic widespread endothelial deposition of hantavirus antigens in an identical pattern to that seen in current cases of HPS was found in various tissues. The largest amounts of antigen were in the lungs, however.[9]

Discussion

Hantaviruses are a group of viruses that belong to the Bunyaviridae family and were previously known to cause illness primarily in Asia and Europe.[10,11] In the severe form, known as hemorrhagic fever with renal syndrome, hantaviral infection results in fever, renal failure, thrombocytopenia, and hemorrhage.[11] Pulmonary edema has been an infrequent but known complication of hemorrhagic fever with renal syndrome.[9,12] In contrast, pulmonary features have been a distinguishing characteristic of the cases identified in the Southwest.[1,5,6,13]

Although studies conducted before the HPS outbreak have demonstrated both the presence of hantavirus in rodents and hantavirus antibodies in low prevalence among people in the United States, there had been only three confirmed cases of acute human disease acquired in the United States.[14] Although the HPS cases identified in 1993 were initially thought to represent the first evidence of severe hantavirus-associated disease in the United States, the case reported here, other retrospectively diagnosed cases, and genetic analysis of autopsy tissue from HPS cases provide evidence that this particular strain of hantavirus has been present in a virulent form for more than 15 years.[7,8,15]

The epidemiologic and clinical features of this case bear a striking similarity to previously reported cases of HPS. A unique aspect of this case is the method by which it became recognized. The patient's mother read about the newly discovered hantaviral infections in local newspapers and magazines and recognized the similarity of the clinical course of the cases in the Southwest with that of her son. Without her astute observation and the wide publicity that the HPS outbreak received, the true cause of death in this patient would have remained unknown.

The clinical characteristics of this case are consistent with a case series of the first 17 reported cases of confirmed HPS.[13] The six most common prodromal symptoms identified in the case series, fever, myalgia, headache, cough, vomiting, and chills, were all present in this case. The duration of symptoms in this case (4 days) is also consistent with that in the other reported cases (median, 4; range, 2 to 15).

The physical findings of this patient were similar to those of the southwestern cases reported in 1993. Fever, hypotension, tachypnea, tachycardia, rales, and mottled extremities were common findings in previously reported cases of HPS; all of these were present in this patient.

Important laboratory results in this patient were leukocytosis, hemoconcentration, thrombocytopenia, increased prothrombin and partial thromboplastin times, a mildly elevated creatinine level, low oxygen saturation, acidosis, and mild proteinuria. These abnormalities, as well as the abnormal chest radiograph from this patient, were consistent with HPS.

The pathologic findings and the overall pattern of histologic and hematologic findings in this case are consistent with those seen in typical cases of HPS.[6,9,16] Immunostaining of patient tissues with cross-reactive monoclonal antibody and *Sin Nombre* virus-specific polyclonal serum provided definitive evidence of HPS.

Previous analysis for predictors of mortality among the first reported cases of HPS found that a combination of a hematocrit greater than 0.56 (56%) and a partial thromboplastin time of greater than 54.4 seconds predicted death with 100% sensitivity and specificity.[13] These two laboratory findings were also noted in the current fatal case.

Epidemiologic studies in the Four Corners region have identified contact with rodents and their excreta as important risk factors for HPS.[2,5,17] This patient, like the patients in the more recently identified cases, lived in a rural setting and engaged in activities that would have enhanced contact with the rodents that were readily observed around his dwelling. Little is known about the patient's activities or whereabouts during his travels to California. Because HPS has been confirmed in regions that the patient is likely to have crossed during his travels (Arizona, California, Nevada, and Utah), exposure en route cannot be excluded.

This case also documents the presence of clinically typical HPS confirmed from autopsy tissue obtained 13 years before the 1993 outbreak. Although there have been only a small number of retrospectively identified confirmed cases of HPS, these cases provide evidence that sporadic cases of HPS are likely to have been occurring for many years at an unknown frequency. The cluster of HPS cases identified in 1993 was most likely due to environmental changes that allowed for increased contact between humans and rodents and their excreta. Continued education of health care providers regarding the clinical and epidemiologic characteristics of this syndrome and the need to report suspected cases of HPS to local health departments should help provide a more thorough understanding of this disease and ways to prevent or treat it more effectively.

To assist health care professionals, the California Department of Health Services has published a medical information sheet that summarizes the clinical features of HPS and that is designed to assist in evaluating cases of possible HPS.[18] A question-and-answer sheet is also available that is designed to address common questions that the general public might have concerning HPS and ways to prevent infections.[19] Recommendations for reducing the risk of hantavirus exposure have been published by the California Department of Health Services and the Centers for Disease Control and Prevention.[20,21] Copies of these documents are available by contacting the state or local health departments in California.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC): Outbreak of acute illness—Southwestern United States, 1993. MMWR 1993; 42:421-424

2. CDC: Update: Outbreak of hantavirus infection—Southwestern United States, 1993. MMWR 1993; 42:477-479

3. Nichol ST, Spiropoulou C, Morzunov S, et al: Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993; 262:914-917

4. CDC: Hantavirus pulmonary syndrome—United States, 1993. MMWR 1993; 43:45-48

5. Shefer AM, Tappero JW, Bresee JS: Hantavirus pulmonary syndrome in California: Report of two cases and investigation. Clin Infect Dis 1994; 19:1105-1109

6. Zaki SR, Kahn AS, Goodman RA, et al: Retrospective diagnosis of hantavirus pulmonary syndrome, 1978-1993: Implications for emerging infectious diseases. Arch Pathol Lab Med 1996; 120:134-139

7. Zaki SR, Albers RC, Greer PW, et al: Retrospective diagnosis of a 1983 case of fatal hantavirus pulmonary syndrome. Lancet 1994; 343:1037-1038

8. CDC: Update: Hantavirus pulmonary syndrome—United States, 1993. MMWR 1993; 42:816-820

9. Zaki SR, Greer PW, Coffield LM, et al: Hantavirus pulmonary syndrome: Pathogenesis of an emerging infectious disease. Am J Pathol 1995; 146:552-579

10. Haemorrhagic fever with renal syndrome: Memorandum from a WHO meeting. Bull World Health Organ 1993; 61:269-275

11. Bruno P, Hassell LH, Brown J, Tanner W, Lau A: The protean manifestations of hemorrhagic fever with renal syndrome: A retrospective review of 26 cases from Korea. Ann Intern Med 1990; 113:385-391

12. Giles RB, Sheedy JA, Ekman CN, et al: The sequelae of epidemic hemorrhagic fever with renal syndrome: A note on causes of death. Am J Med 1954; 16:629-638

13. Duchin JS, Koster FT, Peters CJ, et al: Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994; 330:949-955

14. Glass GE, Watson AJ, LeDuc JW, Childs JE: Domestic cases of hemorrhagic fever with renal syndrome in the United States. Nephron 1994; 68:48-51

15. Spiropoulou CF, Morzunov S, Feldmann H, Sanchez A, Peters CJ, Nichol ST: Genome structure and variability of a virus causing Hantavirus pulmonary syndrome. Virology 1994; 200:715-723

16. Nolte KB, Feddersen RM, Foucar K, et al: Hantavirus pulmonary syndrome in the Unites States: A pathologic description of a disease caused by a new agent. Hum Pathol 1995; 26:110-120

17. Childs JE, Ksiazek TG, Spiropoulou CF, et al: Serologic and genetic identification of *Peromyscus maniculatus* as the primary rodent reservoir for a new hantavirus in the southwestern United States. J Infect Dis 1994; 169:1271-1280

18. Medical Information Fact Sheet: Hantavirus-Associated Infection in California. Sacramento, Calif, Department of Health Services, August 6, 1993

19. Hantavirus Illness and How to Avoid It: Common Questions and Their Answers. Sacramento, Calif, Department of Health Services, August 6, 1993

20. Hantavirus Infection—California: Recommendations for Risk Reduction. Sacramento, Calif, Department of Health Services. August 11, 1993

21. CDC: Hantavirus infection—Southwest: Ir . rim recommendations for risk reduction. MMWR 1993; 42:1-13

Treatment of a Patient With an Undefined Hypercoagulable State With Long-Term Low-Molecular-Weight Heparin

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LOW-MOLECULAR-WEIGHT (LMW) heparins, the catalytically active cleavage products of standard unfractionated heparin, have many favorable pharmacokinetic features. These include excellent bioavailability, a long plasma half-life, and a predictable dose-response relationship. Two LMW heparin products, enoxaparin sodium and dalteparin sodium, have been approved in the United States for the postoperative prophylaxis of deep venous thrombosis in patients having general surgical and orthopedic therapy. Compared with standard postoperative prophylactic regimens with unfractionated heparin, LMW heparin therapy has been shown to be equally efficacious and without notable bleeding complications.[1-3] It has also been shown to be at least as effective as a continuous infusion of unfractionated heparin for the immediate management of documented venous thrombosis before treatment with warfarin sodium.[4,5] In this setting, LMW heparin therapy may decrease hospital stays and minimize monitoring and nursing costs.

Although not currently approved for extended use, LMW heparins have been reported to be effective in various situations. For example, in patients with contraindications to warfarin, therapy for three to six months with LMW heparin after deep venous thrombosis has provided protection against early recurrent thromboses equivalent to conventional warfarin therapy[6] or fixed doses of unfractionated heparin.[7] The effectiveness of LMW heparin in preventing late recurrent events, however, remains a question.[6] In patients with the nephrotic syndrome treated for four months to four years, the daily intravenous administration of enoxaparin is effective in preventing an initial thromboembolic event, without hemorrhagic complications and with cost savings when compared with a nontreatment option.[8] Several studies have shown that antenatal and puerperal LMW heparin therapy successfully prevents thromboembolic events and fetal loss in

(Dobie SA, Ellsworth AJ, Linenberger ML: Treatment of a patient with an undefined hypercoagulable state with long-term low-molecular-weight heparin. West J Med 1996; 164:350-353)

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ABBREVIATIONS USED IN TEXT

aPTT = activated partial thromboplastin time
BMD = bone mineral density
DEXA = dual-energy x-ray absorptiometry
INR = international normalized ratio
LMW = low-molecular-weight

pregnant women with a history of severe recurrent thrombotic episodes.[9-12]

A major concern of extended therapy with LMW heparin is the possible risk of the osteopenia and pathologic fractures seen with prolonged unfractionated heparin use. Two studies that involved treatment for as long as six months reported the preservation of bone density in patients receiving LMW heparin.[7,9] The effects of longer LMW heparin use on bone density have not been defined.

The extended use of LMW heparin to prevent recurrent events in patients with previous thromboses and an underlying hypercoagulable state has not been reported. In this case presentation, a man had an undefined hypercoagulable state and multiple recurrent venous thromboembolic events. His course included recurrent episodes of deep venous thrombosis and a pulmonary embolism while on high-intensity warfarin therapy and an antiplatelet agent. Subsequent therapy with unfractionated heparin caused a substantial loss of bone density. Long-term maintenance therapy with enoxaparin, however, has resulted in the stabilization of bone density, protection against recurrent events, and no incidence of hemorrhage.

Report of a Case

The patient, a 31-year-old man, first presented to the Family Medical Center, University of Washington School of Medicine, in August 1988. He had a distant history of unexplained deep venous thrombosis of the lower extremities in 1979, at 22 years of age, treated with continuous heparin infusion that was followed by warfarin therapy for 18 months. In March 1987, a right calf deep venous thrombus developed that was treated in the same manner; warfarin therapy was continued for 15 months. In August 1988, within a month of discontinuing warfarin, he had an upper gastrointestinal hemorrhage from peptic ulcer disease. He did well until June 1989, when he had a left calf deep venous thrombus. He was again anticoagulated immediately with heparin, followed by 15 months of warfarin therapy, which was discontinued because of concern about the increased risk of gastrointestinal hemorrhage.

In January 1991, four months after discontinuing warfarin, the patient presented with abdominal pain. Laparotomy revealed bowel infarction from mesenteric venous thrombosis, requiring the resection of 120 cm of jejunum. An upper extremity venous duplex study also showed thrombi in his right subclavian, axillary, and brachial veins. Evaluation revealed no evidence of malignancy, myeloproliferative disorder, or nephrotic syndrome. There was no evidence of antiphospholipid or anticardiolipin antibodies; no deficiencies of antithrombin III, protein C, or protein S; and no detectable abnormalities of plasminogen or fibrinogen. He was anticoagulated immediately with unfractionated heparin and subsequently maintained on a warfarin regimen with a prothrombin time expressed as an international normalized ratio (INR) of 3 to 4, the plan being that this therapy would be lifelong.

In June 1992, 18 months later, while on therapeutic doses of warfarin, the patient had an upper gastrointestinal hemorrhage. Endoscopy revealed mucosal ischemia, and angiography demonstrated ileomesenteric venous thrombi. He was managed immediately with continuous intravenous heparin and was converted to long-term treatment with ticlopidine hydrochloride and warfarin, with his warfarin dose adjusted to maintain an INR of 4 to 4.5.

In April 1993, the patient presented with cough and hemoptysis. A ventilation-perfusion lung scan showed considerable perfusion defects without corresponding ventilation defects. Pulmonary angiography confirmed multiple pulmonary emboli. New lower extremity thrombi were demonstrated on venogram. A Greenfield filter was placed in the inferior vena cava, and again the patient was anticoagulated with a continuous intravenous infusion of standard heparin. As high-intensity warfarin therapy had clearly failed, the patient was treated long term with ticlopidine and self-administered, twice-a-day subcutaneous unfractionated heparin. The heparin dose was adjusted to maintain a mid-interval activated partial thromboplastin time (aPTT) in the 80- to 90-second range (60 to 90 seconds corresponding with heparin plasma concentrations of 0.2 to 0.4 U per ml, or 1.7 to 2.5 times the mean normal of 30 seconds). At initiation of this regimen, a bone densitometry study was done using the hologic dual-energy x-ray absorptiometry (DEXA) technique. It revealed a mean trabecular bone mineral density (BMD) at the spine of 0.907 grams per cm^2. There was no osteopenia noted.

In October 1993, despite therapeutic doses of heparin, the patient again presented with evidence of pulmonary embolism. His heparin dose was adjusted and monitored to ensure a mid-dose aPTT of 90 to 110 seconds (mean normal of 30 seconds). After six months of twice-a-day subcutaneous unfractionated heparin, repeat bone densitometry by the DEXA technique revealed substantial trabecular osteopenia, with a mean BMD at the spine of 0.816 grams per cm^2, representing a 23.15% decrease over the six months of therapy with unfractionated heparin. Cortical bone density measured by the DEXA technique at the left wrist showed no osteopenia, with an average BMD of 0.669 grams per cm^2.

Because of the progressive bone loss, the patient agreed to trial therapy with the LMW heparin enoxaparin. Although monitoring has not been routinely recommended for LMW heparin therapy, a therapeutic dosage of enoxaparin was ensured by monthly documentation of four-hour postdose anti-factor Xa levels of between 0.7 and 0.9 IU per ml. The average dose has been 70 mg twice a day. Continuing this regimen, he has had neither

thrombotic events nor gastrointestinal or other bleeding complications.

Bone density was reevaluated by the DEXA technique in April 1994, four months after changing from unfractionated heparin to enoxaparin and six months after the previous study. The mean trabecular BMD was essentially unchanged (0.847 grams per cm^2), and there was a mild increase in the cortical bone density, with a mean cortical BMD of 0.690 grams per cm^2.

The patient has continued to do well. Subsequent bone densitometry studies as measured by the DEXA technique in May 1995 revealed the mean trabecular bone density at the spine to be 0.849 grams per cm^2, which is unchanged from his April 1994 examination. Similarly, the cortical bone density remained stable with a mean BMD of 0.700 grams per cm^2.

During this time, further studies were done to identify an underlying primary hypercoagulable state. Repeat assays of total and free protein S antigen levels and protein C activity and antigen levels were normal. Additional studies revealed the following: no evidence of the specific point mutation in the factor V gene (Arg^{506} to Gln) that is associated with resistance to activated protein C[13]; no evidence of occult paroxysmal nocturnal hemoglobinuria, as determined by the normal expression of CD59 on the surface of peripheral blood leukocytes; no evidence of altered basal fibrinolytic activity, as demonstrated by normal plasma levels of plasminogen activator inhibitor type 1 activity and tissue plasminogen activator activity; and no evidence of an occult myeloproliferative disorder, as suggested by a persistently normal peripheral blood hemogram and the lack of erythropoietin-independent colony growth in peripheral blood progenitor cell culture assays.

Discussion

The patient described here suffers from an underlying hypercoagulable process, with a 14-year history of frequent spontaneous thromboembolic events involving unusual anatomic sites. Despite an extensive search for abnormalities associated with a primary hypercoagulable state and for occult causes of a secondary hypercoagulable state, the cause of this patient's disorder remains unknown. Of great concern was the ineffectiveness of high-intensity warfarin plus antiplatelet therapy in preventing recurrent life-threatening thromboembolic events.

Between 2% and 7% of patients with spontaneous deep venous thrombosis will experience recurrent episodes requiring long-term anticoagulant therapy.[14-16] Whereas oral warfarin remains the treatment of choice for limited or indefinite anticoagulation, therapeutic doses of subcutaneous unfractionated heparin have been shown to be as effective as warfarin in preventing recurrent events after an episode of deep venous thrombosis.[17] Therapeutic unfractionated heparin use may also be associated with potentially fewer bleeding complications.[18] Because of the costs and inconvenience of daily injections, however, long-term subcutaneous heparin therapy has been reserved for patients who have recurrent deep venous thrombosis despite adequate anticoagulation with warfarin (as documented by INRs of 4 to 4.5) or for patients with contraindications to warfarin therapy.[17] Unfortunately, long-term therapy with unfractionated heparin results in a substantial loss of bone density in as much as a third of patients.[19-22] Thus, an effective and safe alternative to the use of warfarin and unfractionated heparin is highly desirable for these patients.

The patient in this report continued to have thromboembolic events while on high-intensity warfarin therapy combined with ticlopidine. Although he did not have a recurrent event on higher-dose subcutaneous unfractionated heparin combined with ticlopidine, he required frequent monitoring and twice-a-day injections and, more important, he suffered considerable trabecular bone density loss. He has now been using subcutaneous enoxaparin for 28 months, with documented stabilization of his bone density and without recurrent thromboembolic events, side effects, or bleeding complications.

This patient's course, together with previous experience with limited-duration therapy with LMW heparins,[7,9-12] suggests that these agents should be strongly considered as an effective alternative to unfractionated heparin. The LMW heparins have great promise as agents for prophylactic and therapeutic anticoagulation. More work is needed to replicate and extend the findings of this report on the long-term use of LMW heparin in persons with recurrent thromboembolic disease for whom warfarin therapy is contraindicated or ineffective.

REFERENCES

1. Colwell CW Jr, Spiro TE, Trowbridge AA, et al: Use of enoxaparin, a low-molecular-weight heparin and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement—A clinical trial comparing efficacy and safety—Enoxaparin Clinical Trial Group. J Bone Joint Surg Am 1994; 76:3-14 [erratum published in J Bone Joint Surg Am 1994; 76:4741]

2. Nurmohamed MT, Rosendaal FR, Büller HR, et al: Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: A meta-analysis. Lancet 1992; 340:152-156

3. Hirsh J, Levine MN: Low molecular weight heparin. Blood 1992; 79:1-17

4. Simonneau G, Charbonnier B, Decousus H, et al: Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med 1993; 153:1541-1546

5. Hull RD, Raskob GE, Pineo GF, et al: Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326:975-982

6. Pini M, Aiello S, Manotti C, et al: Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost 1994; 72:191-197

7. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C: Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71:7-11

8. Rostoker G, Durand-Zaleski I, Petit-Phar M, et al: Prevention of thrombotic complications of the nephrotic syndrome by the low-molecular-weight heparin enoxaparin. Nephron 1995; 69:20-28

9. Melissari E, Parker CJ, Wilson NV, et al: Use of low molecular weight heparin in pregnancy. Thromb Haemost 1992; 68:652-656

10. Gillis S, Shushan A, Eldor A: Use of low molecular weight heparin for prophylaxis and treatment of thromboembolism in pregnancy. Int J Gynaecol Obstet 1992; 39:297-301

11. Rasmussen C, Wadt J, Jacobsen B: Thromboembolic prophylaxis with low molecular weight heparin during pregnancy. Int J Gynaecol Obstet 1994; 47: 121-125

12. Wahlberg TB, Kher A: Low molecular weight heparin as thromboprophylaxis in pregnancy (Letter). Haemostasis 1994; 24:55-56

13. Dahlback B: Inherited thrombophilia: Resistance to activated protein C as a pathogenic factor of venous thromboembolism. Blood 1995; 85:607-614

14. Hirsh J: Heparin. N Engl J Med 1991; 324:1565-1574

15. Hull R, Delmore T, Genton E, et al: Warfarin sodium versus low-dose heparin in the long term treatment of venous thrombosis. N Engl J Med 1979; 301:855-858

16. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BO, Albrechtsson U: Need for long-term anticoagulant therapy in symptomatic calf-vein thrombosis. Lancet 1985; 2:515-518

17. Hull R, Delmore T, Carter C, et al: Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med 1982; 306:189-194

18. Levine M, Hirsh J: Hemorrhagic complications of anticoagulant therapy. Semin Thromb Hemost 1986; 12:39-57

19. Dahlman TC: Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol 1994; 168:1265-1270

20. Ginsberg JS, Kowalchuk G, Hirsh J, et al: Heparin effect on bone density. Thromb Haemost 1990; 64:286-289

21. Ginsberg JS, Hirsh J: Use of anticoagulants during pregnancy. Chest 1989; 95:156S-160S

22. Barbour LA, Kick SD, Steiner JF, et al: A prospective study of heparin-induced osteoporosis in pregnancy with bone densitometry. Am J Obstet Gynecol 1994; 170:862-869

Bartender's Hand
An Unusual Form of Occupational Cumulative Trauma Disorder

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CUMULATIVE TRAUMA DISORDER, also called repetitive strain injury, repetitive motion disorder, or overuse syndrome, encompasses a spectrum of disorders that arise from the overuse of the joints and soft tissue structures of the extremities. Included in this spectrum are such diverse clinical disorders as carpal tunnel syndrome, tenosynovitis, epicondylitis, hand-arm vibration syndrome, de Quervain's disease, and the less-well-defined chronic upper extremity pain syndrome.[1] What unifies these various diagnoses is the hypothesis that repeated biomechanical stresses are responsible for tissue microtrauma, causing local inflammation, inhibiting function, and producing pain.[2]

Occupational cumulative trauma disorders have important effects on workers, their employers, and society in general. Most working adults obtain their medical care from primary care physicians, who should be able to recognize work-related musculoskeletal disorders. Failure to do so can result in substantial losses from decreased productivity, lost work time, inappropriate management, and even disability. An accurate occupational history is crucial to the proper diagnosis.

Several unusual variants of occupational cumulative trauma disorder have been described. These include endoscopist's thumb,[3] mouse joint,[4] and potato harvester's footdrop.[5] The following case report describes another atypical presentation of an occupational cumulative trauma disorder in a bartender. To our knowledge, this is the first reported case of such a disorder in this job category.

(David AM, Taiwo OA: Bartender's hand—An unusual form of occupational cumulative trauma disorder. West J Med 1996; 164:353-354)

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Report of a Case

The patient, a 30-year-old left-handed man, was seen at the Yale-New Haven (Connecticut) Occupational and Environmental Medicine Clinic because of left thumb pain. The pain was located at the base of the thumb and had been gradually increasing over the previous six weeks. Movement made the pain worse. There was no accompanying paresthesia. The joints were not swollen. Occasionally the pain would be accompanied by locking of the third, fourth, and fifth digits of the left hand. No loss of strength was noted. The patient did not recall any antecedent trauma to the hand.

The medical history was unremarkable. A review of systems failed to elicit any systemic symptoms.

The patient was a bartender. His job involved the use of a beverage gun to dispense soda and water. He held the beverage gun in his left hand with the second to fifth digits curled around the base of the gun while the thumb was positioned over the trigger. By exerting sufficient pressure on the trigger with his left thumb, beverage flow could be activated. Relaxing the pressure on the trigger would stop the flow of liquid. He worked about 48 hours a week, using the beverage gun frequently throughout his workshift.

Examination of his hand revealed tenderness at the base of the proximal phalanx of his left thumb. He also had mild tenderness of the metacarpophalangeal (MCP) and proximal interphalangeal (IP) joints of the third, fourth, and fifth fingers. No nodules were felt. No joint effusion was noted. Range of motion was preserved, but there was tenderness with flexion of the MCP and IP joints of the left thumb. Grip strength was good. No sensory or motor deficits were demonstrated. An x-ray film of the hand was unremarkable.

The patient was diagnosed as having flexor tendinitis of the flexor pollicis longus, flexor pollicis brevis, and flexor digitorum sublimis of the third, fourth, and fifth digits with concomitant stress of the ulnar collateral ligament. He was treated conservatively with a nonsteroidal anti-inflammatory agent and physical therapy. Job modification was discussed with his employer, who agreed to switch him from bartending to waiting on tables. His symptoms started to resolve gradually after he stopped using the beverage gun. Six weeks after the job change, he was completely asymptomatic.

Discussion

This case depicts an unusual variant of an occupational cumulative trauma disorder. The patient's thumb pain likely resulted from repeated flexion of the thumb at both the MCP and IP joints against the resistance of the beverage gun trigger. "Locking" of his third, fourth, and

ABBREVIATIONS USED IN TEXT

IP = interphalangeal
MCP = metacarpophalangeal

fifth digits likely occurred from inflammation of the flexor tendons from repeated friction and pressure against the barrel of the beverage gun.

Other features of this case consistent with an overuse syndrome include the gradual onset, the anatomic specificity of the findings as it related to the proposed mechanism of injury, the absence of a systemic disease or other rheumatologic condition to explain the patient's symptoms and signs, and the gradual but complete resolution of symptoms after cessation of the repetitive activity.

Occupational cumulative trauma disorders can present in an atypical fashion, as this case demonstrates. To make the appropriate diagnosis, it is essential to perceive the association between repetitive stress from work practices and the resultant clinical presentation. This can only be achieved with a thorough occupational history. Obtaining the job title or general job description alone may not provide sufficient information to delineate the relationship of the patient's symptoms with specific occupational tasks.[6] It is more desirable to elicit a detailed description of those activities that may relate to symptoms. Often it is advisable to have the patient "act out" the work activity. Alternately, it might be productive to visit the work site while the patient is working and directly observe the patient's work practices. Frequently, as in this case, there are no objective tests to aid in the diagnosis. Hence, the correct identification of the problem rests on an accurate occupational history and clinical examination.

The medical management of occupational cumulative trauma disorders is often conservative, consisting of rest, nonsteroidal anti-inflammatory agents, and physical therapy. In conjunction with this regimen, an evaluation of the work site and work practices is crucial so that the appropriate ergonomic and job modifications can be instituted.

REFERENCES

1. Williams R, Westmorland M: Occupational cumulative trauma disorders of the upper extremity. Am J Occup Ther 1994; 48:411-420

2. Parker KG, Imbus HR: Body tissues and fatigue, chap 1, Cumulative Trauma Disorders. Boca Raton, Fla, Lewis Publishers, 1992, pp 25-27

3. Buschbacher R: Overuse syndromes among endoscopists. Endoscopy 1994; 26:539-544

4. Norman LA: Mouse joint—Another manifestation of an occupational epidemic? West J Med 1991; 155:413-415

5. Garland H: The occupational factor in compressive lesions of peripheral nerves. J Univ Leeds Med 1955; 4:63-66

6. Rosenstock L, Cullen MR: Textbook of Clinical Occupational and Environmental Medicine. Philadelphia, Pa, WB Saunders, 1994, pp 3-6

Topics in Primary Care Medicine

Clinical Breast Examination

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Clinical breast examination (CBE) continues to be important despite the widespread use of mammography. About half of breast cancers are still found by patients themselves, so clinicians must use CBE to understand what patients are finding on their bodies. In addition, CBE by health professionals is still the only way that more than 10% of breast cancers are detected.[1,2]

Clinical breast examination is a rapid procedure. In two to three minutes,[3] a clinician can decide whether a woman's breasts are as expected in the dual context of what is normal for all women and what would be usual changes given the patient's personal history.

Most written descriptions of CBE focus on the sequential steps of the examination—with occasionally a discussion of how to palpate—but omit the mental checklist a clinician should review to understand the examination. In this essay, I suggest points that physicians should consider during CBE. These are not all inclusive, but any CBE should, as a minimum, include the topics outlined here.

Role of Risk Factors in the Routine Clinical Breast Examination

Statistics cannot guide the conclusions drawn from any specific routine breast evaluation. Despite their use to shape our understanding of breast cancer and to guide future research, statistics have little practical value during an individual routine examination. There is not sufficient difference between the yield of CBE in a high-risk patient and that in a low-risk patient to use risk factors to decide whether a CBE is within normal limits. Most breast cancers occur in women who have no known risk factors, so that the absence of risk factors is not a reliable basis to decide not to proceed with the further evaluation of a possible area of concern. Likewise, although a woman may be at high risk for breast cancer, "high risk" is a relative term describing the likelihood of cancer over a lifetime.[4] In this context, even for a high-risk patient, each clinical evaluation represents one chance out of a lifetime that a single event will be recognized. Thus, even for high-risk women, the chance of finding a breast cancer during any single breast examination is low.

Taking a history of personal risk factors acknowledges the concerns of the patient and prepares the physician to counsel her concerning future expectations. Taking a history is also the way to learn what a patient may have felt during a self-examination. These aspects of caring for the patient should not, however, be confused with bases to decide whether a woman's examination is within normal limits. Every breast examination should be done in the same manner for all women with equal attention to detail and an equal level of suspicion.

Components of a Clinical Breast Examination

Observation of the breast, the palpation of local and regional lymph nodes, and palpation of the breast are the components of a CBE. During a complete breast examination, the examiner should consider the following: Is the breast being examined in a standardized way that is likely to detect possible abnormalities in any part of the breast? Are findings consistent with the known, normal structure of the breast? Are the breasts symmetric? Are findings on palpation consistent with a woman's life history?

Observation of the Breast

Breast examination begins with a static observation; the clinician observes the skin for rashes, discoloration, or ecchymosis as well as any visible lumps, swelling, or changes in the skin.

Next, the clinician observes the motion of the breast as the patient changes position. During changes from a supine to a sitting position, the gland moves, changes shape, shifts its position, and exerts tension on the suspensory ligaments that connect the breast to the overlying skin and the underlying chest wall muscles. Normally this tension is distributed evenly, and the skin of the breast pulls in a smooth contour. Irregularity of the tension on the skin of the breast causes dimpling and indicates that something abnormal has disturbed the normal shifting and flexibility of the breast.

Dimpling or a visible irregularity of tension on breast skin, if it exists, is accentuated by pulling on the mammary gland with traction from the underside. Such traction is created when the patient raises her arm over her head, thereby moving the insertion of the pectoral muscle upward or, alternatively, when she flexes her pectoral muscles, which will pull the muscle tighter and the deep surface of the breast upward. Relative, deep tension can also be created by having the patient lean forward. This method uses gravity to pull the breast and skin away from the pectoral muscle and is particularly useful in a woman who has large breasts.

(Goodson WH III: Clinical breast examination. West J Med 1996; 164:355-358)

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Palpation of Lymph Nodes

Lymph nodes should be sought above and below the clavicles and in the axillae. The palpation of lymph nodes is influenced by the position of the patient and the amount of body fat. Axillary lymph nodes, for example, are more easily felt when a woman sits erect and the weight of her breast pulls axillary tissue, particularly high nodes, down to an accessible position. Body fat can obscure small nodes, although small axillary nodes are sometimes encountered in persons who have frequent small cuts from pets or perform repeated wet or dirty tasks such as gardening.

Palpation of the Breast

Palpation of the breast is the most important and least discussed part of CBE—that is, the motions of breast examination are well described, but the interpretation of the findings is only vaguely discussed. For this reason, several key questions about palpation are posed and discussed.

How does the position help palpation of the breast? In general, a clinician learns more by observing the breast and palpating nodes when a woman is sitting and palpating the breast when she is supine. Occasionally, however, a mass will best be felt during bimanual palpation when the patient is sitting—that is, one hand supports the breast while the other palpates.

Whether a woman is sitting or lying, the physician usually asks her to hold her hands behind her head during palpation of the breast. The result is that the breast is pulled flatter, which makes any specific part of the breast "thinner" and easier to palpate.

What pattern should be used for palpating the breast? The pattern of palpation determines whether a thorough examination is done. Accessory breast tissue can be encountered as far cephalad as the anterior shoulder or as far caudal as the groin, but in general, a complete CBE covers from the clavicle to the inframammary fold and from the midaxillary line to the middle of the sternum. Studies of breast self-examination have shown that radial or circular patterns tend to focus attention on the area immediately around the nipple and areola and to overlook peripheral areas.[5] A more complete breast examination is done when the fingers cover the breast in sequential vertical strips from the clavicle to the inframammary fold starting at the midaxillary line and moving medially (Figure 1).[5] Although these are studies of self-examination, there is no reason to think that clinicians will not make similar errors if there is not meticulous attention to palpating all areas of breast tissue.

How should fingers move during palpation? Palpation can be done several ways: using two or three fingers in small circular motions with varying pressure to sense the consistency of breast tissue at different depths under the skin; rolling tissue between two fingers as though alternating between the "j" and the "k" on a keyboard or the "A" and "B" on a piano; and sliding the fingers over the surface of the breast with or without some form of skin lubrication with water, soap, alcohol, or sheets of silicone-coated rubber. Each of these techniques has its usefulness, and experienced clinicians tend to use them in combination. It is also sometimes useful to stabilize the breast with a hand on the nipple areolar complex, using the other hand to examine each quadrant of the breast in a smaller strip pattern.

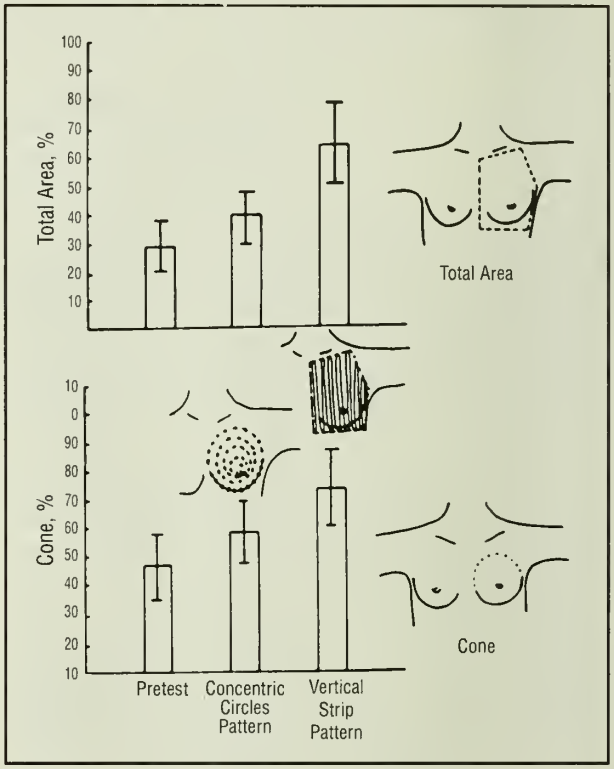

Figure 1.—The portion of the breast tissue evaluated during breast self-examination is influenced by the examination pattern. A vertical strip pattern results in a larger portion of the breast area being covered. It is probable that physicians also fail to examine substantial portions of the breast if they assume that the nipple is the center of the breast. The vertical bar represents the standard deviation. (Reprinted with permission from Saunders et al.[5])

How Density and Nodularity Affect a Clinical Breast Examination

When palpating the breasts, clinicians always feel a composite of tissue that includes skin, subcutaneous fat, gland, muscle, and bone (Figure 2).[6] Two properties of this composite can be described: density or firmness that indicates the degree to which breast tissue can be compressed or deformed by the pressure of the examiner's hand; and nodularity or bumpiness that indicates the degree to which the surface of the breast varies between smooth and irregular. A less dense breast tends to be more nodular, and vice versa.[7]

Density can be defined by the degree to which the outline of ribs can be felt through the gland tissue of the breast. In most women, it is possible to feel ribs through the upper outer quadrant of the breast tissue (the area of

greatest density in most women); in some women, it is possible to feel only a suggestion of the shape of the ribs in this area; and in some women it is impossible to feel the ribs at all.[7] Clinicians can confirm that a rib is being felt by following the edge of the rib from an easily accessible area such as beside the sternum or in the axilla. The use of the ribs as a reference point reduces the possibility of confusing ribs palpated through the breast tissue for "lumps," and because ribs are always present, it gives an objective way to compare the density of one woman's breasts with that of another's.

Nodularity is more subjective, although the extremes are relatively obvious. A smooth breast that has literally no nodularity is extremely uncommon, but it does exist. The other extreme, equally uncommon, is a breast that has multiple hard lumps and therefore many areas of possible concern. The breasts of most women are between these extremes, with some diffuse nodularity over the entire breast. With sufficient compression, breast tissue, and particularly subcutaneous fat, can be felt in smaller segments or sections and interpreted as lumpy. By focusing on density and nodularity as distinct characteristics of breast tissue, a clinician will be aware of the amount of pressure exerted during the examination and therefore avoid interpreting normal findings as abnormal.

The presence of nodularity and density does not indicate disease. There is no correlation between either nodularity or density and the presence of underlying disease that might indicate an increased risk of cancer.[7] These descriptors help physicians avoid broad or inclusive terms such as "fibrocystic" that, though commonly used, are confusing because they have no precise meaning other than as a general impression.[8]

How the Quadrants Differ

Palpation of the breast differs according to the area of the breast being examined. Typically the upper outer quadrant is denser than the upper inner or the lower outer quadrants and much denser than the lower inner quadrant. In addition, the lower and medial parts of the pectoralis major muscle tend to have less bulk, and, therefore, ribs may be more sharply defined during the palpation of breast tissue over these areas. If the breast is large or there is pendulous tissue, the lower edge of the breast where the tissue is folded on itself for prolonged periods of time may thicken into what has been called the inframammary fold.

The central part of the breast, beneath the areola and nipple, reflects the nurturing function of the breast. This is the reservoir from which nursing infants suck milk; it must be distensible and flexible for nursing. For this reason, retroareolar tissue is usually softer than the surrounding breast gland, even the tissue in the lower inner quadrant. Often the gland tissue that borders the areola has a distinctly scalloped or nodular feel.

The Usefulness of Symmetry

Understanding the normal distribution and architecture of the breast helps clinicians anticipate findings on

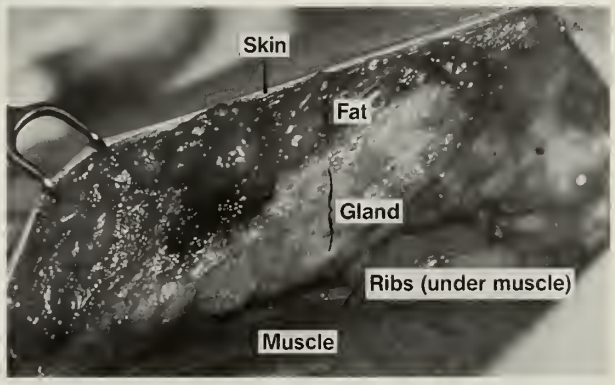

Figure 2.—During palpation, a composite of skin, subcutaneous fat, the breast gland tissue, muscle, and underlying bone of the chest wall is felt. Palpation of the ribs through the breast is a useful way to determine the breast density and avoid mistaking ribs for lumps. (Reprinted with permission from Goodson.[6])

an individual patient. For example, it is not rare for a woman to have some increased density in the upper midportion of her breast, at what is often described as the 12 o'clock position. Fortunately, such less typical distribution of gland tissue tends to be symmetric. If it is not symmetric, the clinician must ask, "Why?"

The assessment of symmetry helps determine whether a specific area of a woman's breast is abnormal or is simply "normal" for her. Symmetry is best evaluated when the clinician examines each breast symmetrically from the same relative position—that is, the clinician walks to both sides of the table to complete the examination from a symmetric perspective (this "walk" is included in the 3-minute screening examination). Results are enhanced when a woman's breasts are dependent toward her side while she is supine.

Obvious exceptions to symmetry are areas of previous surgical therapy. The breast gland tissue under a skin scar can be focally scarred or thickened. Alternatively, if the gland tissue has not been successfully approximated after a previous operation, the area under a scar will be softer, and adjacent areas where tissue of normal consistency resumes can actually feel denser and raise concern that there may be an adjacent "lump."

How Life History Influences Density and Nodularity

Nodularity and looseness of the skin both increase greatly if there have been events when a woman's breasts were larger and then became smaller, such as after pregnancy and lactation when breast engorgement subsides, and the breast feels more nodular. This is not "fibrocystic," and these normal, anticipated changes should not be interpreted as a disease or a "condition." Similar changes are seen after substantial weight loss and when hormonal stimulation of the breasts stops after menopause. Weight gain can obscure nodularity, and the clinician must ascertain that fatty lobules are of uniform density over wide areas of the breast. If a woman uses hormone replacement therapy after menopause, her breasts may increase in density. Premenopausal women

often have increased breast density during the premenstrual period when hormonal levels are high and decreased density when hormonal levels drop as menstruation begins. Such changes should be considered whenever a patient's breasts are being examined.

How to Decide if an Abnormality Exists

Having decided how to position the patient, what pattern of breast examination to use, how to use one's fingers, how to stabilize the breast, how to describe what is felt, and whether findings on palpation are as expected, the clinician must decide whether further evaluation is needed. Obvious lumps that are discrete and distinctly different from surrounding tissue are usually not difficult to identify. They can move within tissue or feel fixed, and like large visible lumps, they are easily perceived as different. Subtle findings are areas that do not move, shift, or compress as anticipated or that are asymmetric relative to the other breast in one of these characteristics or in density or nodularity in general. A common misconception is that clinicians seek lumps and then interpret what the lump or other area is. This assumes that some combination of experience and sensory acuity will lead to the right decision as to whether a specific "lump" might be cancer and therefore warrant a biopsy. It is more productive to consider the breast as an organ with a structure that should make sense in the context of normal breast structure and a woman's life history. Any deviation from expected findings requires further assessment.

What Does Breast Tenderness Signify?

Breast tenderness, which many women report during breast examination, correlates in a general way with breast density.[9] Generalized tenderness is not usually an instructive finding, however, and pain itself is an unusual presentation of cancer.[10] Tenderness during deep palpation is best considered like abdominal discomfort that can be elicited by deep palpation on most persons. Exceptions are sensitivity to light palpation or focal tenderness. With sensitivity to light palpation, possibilities of infection or generalized cancer must be considered. Skin changes are often present in such cases, although cancers that cause skin changes, such as inflammatory cancer, can also be painless. The evaluation of focal tenderness is complicated because the patient, who feels the pain, can repeatedly localize one area. For both sensitivity or focal tenderness, the clinician's task is the same as when these symptoms are not present. The physician examines for areas that have distinct or asymmetric characteristics.[11] In the absence of physical findings, biopsy can be guided only by mammography if an abnormality is detected or by doing a biopsy directed not by palpation or mammography but by the patient's descriptions. There is no best way to decide whether to do a biopsy in these situations, and consultation is often useful.

When the Clinician Cannot Feel What the Patient Feels

Many women are sensitive to minor changes and variations that occur in their own breasts and that are not readily apparent to a clinician. If a woman reports an area of concern that the clinician cannot feel and cannot detect by mammography, it is important to resolve this difference in a way that respects the observation of the patient. Options include the following: repeating the CBE at a brief interval of two or three months and a longer interval of about six months, referring the patient to a surgeon and other physician for examination, and recognizing that the patient may be correct and acknowledging to the patient that she has the right to seek another opinion. Remember that more than half of breast cancers are found by patients themelves.[1,2]

Summary

An astute clinician has an appreciation of the wide variation possible in normal breasts, but anticipates that the palpation of the breasts of an individual woman will be determined by basic facts concerning typical relative distribution of gland tissue, breast symmetry, the influence of life history, and possibly previous surgery. If the findings of a CBE are not as anticipated, the clinician must find out why this is so. This is a different frame of reference from asking whether a given lump or area should be considered suspicious for cancer. The basic questions are whether the findings of a CBE are consistent with typical breast structure and anatomy and in the context of the woman's life history. If these questions can be answered in the affirmative, the examination is complete: if not, further evaluation is necessary.[12,13]

REFERENCES

1. Farwell MF, Foster RS Jr, Costanza MC: Breast cancer and earlier detection efforts—Realized and unrealized impact on stage. Arch Surg 1993; 128:510-514

2. Reeves MJ, Newcomb PA, Remington PA, et al: Determinants of breast cancer detection among Wisconsin (United States) women, 1988-90. Cancer Causes Control 1995; 6:103-111

3. Hoskins KF, Stopfer JE, Calzone KA, et al: Assessment and counseling for women with a family history of breast cancer—A guide for clinicians. JAMA 1995; 273:577-585

4. Mahoney L, Csima A: Efficiency of palpation in clinical detection of breast cancer. Can Med Assoc J 1982; 127:729-730

5. Saunders KJ, Pilgrim CA, Pennypacker HS: Increased proficiency of search in breast self-examination. Cancer 1986; 58:2531-2537

6. Goodson WH 3d: Annual breast examination. *In* Glass RH (Ed): Office Gynecology. Baltimore, Md, Williams & Wilkins, 1992, pp 121-132

7. Goodson WH 3d, Miller TR, Sickles EA, Upton RA: Lack of correlation of clinical breast examination with high-risk histopathology. Am J Med 1990; 89:752-756

8. Love SM, Gelman RS, Silen W: Sounding board: Fibrocystic 'disease' of the breast—A nondisease? N Engl J Med 1982; 307:1010-1014

9. Goodson WH 3d, Mailman R, Jacobson M, Hunt TK: What do breast symptoms mean? Am J Surg 1985; 150:271-274

10. Griffith CDM, Dowle CS, Hinton CP, Blamey RW: The breast pain clinic—A rational approach to classification and treatment of breast pain. Postgrad Med J 1987; 63:547-549

11. Mansel RE: ABC of breast diseases: Breast pain. BMJ 1994; 309:866-868

12. Grady D, Hodgkins ML, Goodson WH 3d: The lumpy breast. West J Med 1988; 149:226-229

13. Donegan WL: Evaluation of a palpable breast mass. N Engl J Med 1992; 327:937-942

This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Editorials

Lightning and Fattening—Evolving Concepts in the Pathogenesis of Preeclampsia

PREECLAMPSIA IS a pregnancy-specific syndrome characterized by hypertension, edema, and proteinuria. More than 300,000 new cases are expected to be identified this year in the United States. The pathophysiology of preeclampsia is poorly understood, and consequently its therapy remains empirical: expedient delivery. Emergent operative and often preterm delivery are the major causes of the increased maternal and neonatal morbidity and mortality associated with preeclampsia. In developed countries, complications arising from preeclampsia are the second leading cause of maternal mortality after motor vehicle accidents. With current management, progression to its convulsive phase, eclampsia, occurs in only 4% to 5% of women with preeclampsia. Nevertheless, its dramatic clinical presentation and life-threatening consequences still make this one of the most feared complications of pregnancy. According to Leon Chesley, a leading scholar of preeclampsia, it was the French author de Sauvages who introduced the clinical description *eclampsia parturientium* in 1739. de Sauvages, in turn, attributed Hippocrates with the term εχλαμψιεσ (*eklampsis*), the Greek word for "lightning," to describe the sudden and unpredictable onset of convulsions recognized since antiquity as a risk in late pregnancy.[1]

Hypotheses that impaired trophoblast invasion, poor placental perfusion, and generalized maternal endothelial cell activation or injury are associated with preeclampsia have been advanced over the past decade.[2] Histochemical studies of the placental beds of preeclamptic women demonstrate impaired trophoblast invasion and the failure of vascular remodeling. Doppler flow studies confirm decreased spiral artery and placental perfusion in this condition. Several markers of endothelial cell dysfunction have been reported in patients with preeclampsia, including decreased circulating levels of prostacyclin and elevated concentrations of endothelin-1, cellular fibronectin, and thrombomodulin. Morphologic and functional evidence of endothelial injury, particularly in glomeruli, also has been documented in women with this disorder. Maternal endothelial cell activation or injury are thought to result in vasospasm, microthrombosis, and vascular permeability. The focus on the endothelial disorder in this syndrome has provided a rationale for trials of low-dose aspirin and other antiplatelet agents for the chemoprevention of preeclampsia. Although this strategy appears to reduce the incidence of preeclampsia in high-risk patients, its efficacy as preeclampsia prophylaxis in general obstetric patients has been disappointing.[3]

As Ms Duda indicates in her review article elsewhere in this issue,[4] many of the mysteries that underlie the cause of preeclampsia reflect our limited understanding of the immunobiology of human pregnancy. The placental bed is a unique immunologic environment in which a natural tolerance exists between two antigenically disparate tissues. The commonly held postulate that maternal immunologic tolerance of the foreign fetus is mediated by the activation of an antigen-blocking system has yet to be substantiated. Despite the search for systemic alterations in immunocompetence and responsiveness during human pregnancy, there is little evidence to support widespread or global effects of pregnancy on the maternal immune system. It should be stressed, however, that laboratory inconsistencies and variation in immune responses among pregnant women pose difficulties in the interpretation of many of these studies. It is generally accepted that total T-lymphocyte concentrations are not altered during pregnancy. Neither do circulating B cell or immunoglobulin (Ig) G, IgM, or IgA concentrations change substantially from prepregnancy values.[5]

Growing evidence supports the opinion that local, rather than systemic, factors are of primary importance in the immune tolerance of pregnancy. The postulated effectors include large granular lymphocytes of maternal origin that rapidly populate the decidua after conception and immunomodulatory proteins, hormones, and cytokines elaborated by either or both maternal and fetal tissues in the placental bed. Of critical importance is the discovery that invading extravillous trophoblasts express a truncated, nonpolymorphic class I-like antigen, HLA-G.[6] This immunologically neutral histocompatibility antigen is postulated to protect the invading trophoblasts from maternal immune recognition while preserving important cell-to-cell interactions that allow these cytotrophoblasts to invade and migrate through the uterine decidua.

Whatever the evasive mechanisms of trophoblast cells in normal pregnancy, the preeclampsia syndrome has long been thought to represent a defect in the normal immunologic cloaking system. Dieckmann, in 1941, referring to earlier work of German investigators, stated that "Eclampsia is due to a hypersensitivity to a protein product which reaches the maternal organism by way of the maternal veins during pregnancy and sensitizes it."[7] Indeed, preeclampsia may arise in clinical situations where an insufficient production of antigen blocking factors (such as in the first pregnancy) results in maternal immune responses and exposes the placenta to injury. A further production of blocking antibodies in later pregnancies might protect the placenta and thus explain the relative immunity of multiparous women to recurrent preeclampsia. This hypothesis is consistent with many epidemiologic observations, several of which are summarized in Duda's review, including the higher prevalence of preeclampsia in first pregnancies, an inverse relationship with length of cohabitation before conception, and an increased risk in couples using barrier contraceptive methods.[4]

Unfortunately, more direct attempts at defining the immunogenetics of preeclampsia have suffered from small

sample sizes and limited statistical power. Whereas the incidence of preeclampsia in daughters of eclamptic women is eightfold greater than in the normal population, the collection of adequate pedigrees has been hampered by the fact that preeclampsia affects only women and tends to be manifest during the first, but not in subsequent, pregnancies. Hence, many of the studies that attempted to link preeclampsia risk with specific marker haplotypes have been inconclusive. One analysis of preeclampsia in adult identical twins revealed no concordant affected pairs and five discordant affected pairs. Random DNA markers in two-generation families with preeclampsia failed to identify positive linkages in an exclusion map. It has been postulated recently that an interaction between fetal and maternal genotypes may be required to produce the preeclampsia syndrome.[8]

Theoretically, both trophoblasts and maternal vascular endothelial cells represent possible targets of immune-mediated cellular injury in preeclampsia. As discussed earlier, fetal syncytiotrophoblast cells lining the placental villi and invasive extravillous cytotrophoblasts that penetrate the decidua and spiral arteries are in direct contact with cells of the maternal host. These fetal cells are semiallogeneic with respect to their host and hence are obvious targets for immunologic aggression. The maternal vascular endothelium, although isogeneic, presents a vast interface between circulating immunocytes and peripheral tissues and is a common target of autoantibodies and immune complexes. The mechanisms responsible for the apparent increase in vulnerability of the vascular endothelium during pregnancy are unknown. The exacerbation of collagen-vascular diseases and enhanced sensitivity to antiphospholipid antibodies during gestation may reflect the dramatic hemodynamic, endocrine, and paracrine alterations that constitute the maternal vascular adaptation to pregnancy.

A failure to activate protective responses, with the development of antifetal antibodies, has been postulated as a mechanism common to early spontaneous abortion and preeclampsia. Lupus anticoagulant, antiphospholipid, and antiendothelial cell antibodies have been identified by enzyme-linked immunosorbent assay in some women with preeclampsia. It has been suggested that these antibodies interfere with endothelial cell function by inhibiting prostacyclin production and stimulating procoagulant synthesis. Other investigators have shown, however, that some sera containing antiphospholipid antibodies actually enhance prostacyclin secretion in endothelial cell cultures. We and others have shown that prostacyclin production by cultured human endothelial cells incubated with plasma or serum from preeclamptic women was substantially greater than by cells exposed to blood from normal pregnant controls.[9] Our data indicated that a factor(s) in preeclampsia plasma could stimulate phospholipase A_2 activity and prostaglandin production in several different cell types. Although this hypothesis is not yet tested, it is conceivable that the same factor(s) could activate platelet thromboxane synthesis and incite vasospasm and thrombosis.

A relatively recent development in studies of preeclampsia is the recognition of abnormal lipid metabolism in affected women, although lipid-laden macrophages were identified in vascular "atherosis" lesions more than 45 years ago. Prepregnancy obesity appears to be a major independent risk factor for the development of severe preeclampsia.[10] Concentrations of fasting serum triglycerides and free fatty acids, measured longitudinally in cohort studies, indicate that elevations in circulating lipid levels antedate clinically recognized preeclampsia by several months.[11] Excessive endothelial cell uptake of free fatty acids can lead to lipid accumulation, cellular dysfunction, and alterations in prostaglandin production. Thus, dyslipidemia associated with preeclampsia also may adversely affect maternal endothelial cell homeostasis and vascular function. Elucidating the role of fatty acids in this syndrome may lead to pharmacologic or dietary interventions that improve maternal and fetal outcomes in this condition.

Finally, Duda makes the important point that two different sets of criteria are needed to define the preeclampsia syndrome.[4] For the purpose of basic and clinical investigation, it is important to define preeclampsia as strictly and specifically as possible, requiring nulliparity, proteinuria, hyperuricemia, and hypertension, as recommended by Chesley,[12] and insisting that the signs resolve within the first 12 postpartum weeks. Establishing stringent diagnostic guidelines allows investigators to dissect the pathogenesis of preeclampsia from that underlying other forms of hypertension in pregnancy. When clinically managing pregnant women, however, it is preferable to overdiagnose preeclampsia rather than overlook mild cases in women whose health can deteriorate without warning.

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REFERENCES

1. Chesley LC: History, chap 2, Hypertensive Disorders in Pregnancy. New York, NY, Appleton-Century-Crofts, 1978, pp 20-22

2. de Groot CJ, Taylor RN: New insights into the etiology of preeclampsia. Ann Med 1993; 25: 243-249

3. Sibai BM, Caritis SN, Thom E, et al: Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women—The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. N Engl J Med 1993; 329:1213-1218

4. Duda J: Preeclampsia: Still an enigma. West J Med 1996; 164: 315-320

5. Feinberg BB, Gonik B: General precepts of the immunology of pregnancy. Clin Obstet Gynecol 1991; 34:3-16

6. McMaster MT, Librach CL, Zhou Y, et al: Human placental HLA-G expression is restricted to differentiated cytotrophoblasts. J Immunol 1995; 154: 3771-3778

7. Dieckmann WJ: Factors influencing eclampsia in pregnant women, chap 14, The Toxemias of Pregnancy. St Louis, Mo, CV Mosby, 1941, pp 250-251

8. Cooper DW, Brennecke SP, Wilton AN: Genetics of preeclampsia. Hypertens Pregnancy 1993; 12:1-23

9. de Groot CJ, Davidge ST, Friedman SA, McLaughlin MK, Roberts JM, Taylor RN: Plasma from preeclamptic women increases human endothelial cell prostacyclin production without changes in cellular enzyme activity or mass. Am J Obstet Gynecol 1995; 172:976-985

10. Stone JL, Lockwood CJ, Berkowitz GS, Alvarez M, Lapinski R, Berkowitz RL: Risk factors for severe preeclampsia. Obstet Gynecol 1994; 83:357-361

11. Lorentzen B, Drevon CA, Endresen MJ, Henriksen T: Fatty acid pattern of esterified and free fatty acids in sera of women with normal and preeclamptic pregnancy. Br J Obstet Gynaecol 1995; 102:530-537

12. Chesley LC: Diagnosis of preeclampsia. Obstet Gynecol 1985; 65: 423-425

Cystic Fibrosis Therapy—Where We Are and How We Got There

THE DIAGNOSTIC CHARACTERISTICS of cystic fibrosis, such as meconium ileus, digestive disorders, and lung disease leading to premature death, have been anecdotally described in folk literature as early as 1650.[1] After its characterization as a distinct disease in the 1930s, cystic fibrosis was suggested to be a recessive inherited disorder.[2] The advances in the understanding of the biochemical nature of the cystic fibrosis defect and the institution of more aggressive mechanical and antibiotic therapies have been instrumental in enhancing the life expectancy and quality of life for patients affected with the disorder. Many of the affected children have now become affected adults with a host of disorders that require therapies distinct from those of the children. Whereas the mean survival age is now between 28 and 30 years, the specter of premature death from respiratory tract infection still looms on the horizon of patients with cystic fibrosis. Although the disease was initially thought to be one of the digestive tract, it quickly became evident that it was the respiratory tract infection that was responsible for more than 95% of all of the morbidity and mortality of cystic fibrosis.

It was the work by di Sant'Agnese and co-workers investigating salt depletion in cystic fibrosis children that showed excessive salt levels in the sweat of these children.[3] Those investigations set the stage for studies of the sweat glands[4] and those of the airways[5,6] some 30 years later. The findings of these studies and those of others have indicated that the basic abnormality underlying cystic fibrosis is a defect both in chloride ion secretion and in sodium absorption. Ultimately it was determined that the defect in chloride ion transport was in the apical membrane of epithelial cells[7] and that it was cyclic adenosine monophosphate-dependent.[8] Subsequent observations indicated that intact calcium- and volume-activated chloride transport pathways are present in the cystic fibrosis epithelium. These observations have been the basis of clinical trials designed to test the potential of nucleotide analogues as chemotherapeutic agents.

The underlying mechanisms of cystic fibrosis were further elucidated in 1989 by the identification and isolation of the gene most closely associated with the disease: the cystic fibrosis transmembrane conductance regulator (*CFTR*). The more than 500 mutations found in this gene have been associated with a spectrum of diseases ranging from severe pancreatic and lung disease to mild disease. It has also been determined that a previously unrelated disease, the chronic bilateral absence of the vas deferens, can result from mutations in the *CFTR* gene.[9,10]

Characterization of the *CFTR* protein has led to the development of therapies based on *CFTR* functional augmentation and on the activation of alternative ion transport pathways. In addition, the isolation of the *CFTR* gene has been the basis of one of the most intensive gene therapy efforts for any inherited disorder. The initial trials that have been designed to test the safety of a given strategy have been complicated by the host immune response.[11] This complication appears to underlie the limited efficacy and the transient expression of the *CFTR* transgene that has been observed regardless of whether the transgene is introduced by adenoviral vectors or by liposomes. These results have presented an obstacle to fulfilling the dream of a gene therapy cure for cystic fibrosis. Although the potential for cystic fibrosis gene therapy has yet to be realized, the progress toward this end has been furthered by support and initiatives by the National Institutes of Health and the Cystic Fibrosis Foundation.

Until the goal of correcting the genetic defect underlying cystic fibrosis can be achieved, the focus must be on other more conventional therapies to enhance the quality of life for adults affected with the disease. The review article by Marelich and Cross elsewhere in this issue makes this point and provides an overview of the present state of the art in the clinical management of cystic fibrosis.[12] Their coverage on the present state of intervention for the management of the cystic fibrosis disorder emphasizes the importance of maintaining an active antibiotic and mucus-clearing regimen for the treatment of all age groups of patients with cystic fibrosis. The development of the deoxyribonuclease therapy for decreasing mucus viscosity has had a substantial effect on the quality of life of cystic fibrosis patients. In addition, clinical trials of ibuprofen have shown a substantial improvement in lung function as a result of decreasing airway inflammation. This treatment will undoubtedly find itself in the mainstream of therapies for this disease in the near future.

As an adjunct to antibiotic therapies, researchers are also developing antibacterial therapies that either modify the host immune response[13] or focus directly on bacterial binding. Because the hallmark bacterium of cystic fibrosis lung infection is *Pseudomonas aeruginosa*, there has been a substantial effort characterizing the *P aeruginosa*-binding sites both in mucus and on airway epithelial cells. Furthermore, we are now gaining a better understanding of the relationship of the modulation of cytokine-mediated inflammation in cystic fibrosis patients. It is clear that the interplay between the proinflammatory interleukin (IL)-8 and anti-inflammatory IL-10 can play a substantial role in defining the inflammatory state of an infected airway.[14] The goal will now be to enhance the levels of IL-10 (which are disproportionately low in fibrocystic airways) and decrease the levels of IL-8 (which are elevated in these airways).

The development of alternative pharmacologic therapies will continue to be necessary while the issues concerning the efficacy of cystic fibrosis gene therapy are being resolved. In fact, it is possible that both gene and pharmacologic therapies can act in concert. In certain cases, a combined approach may even be more appropriate than the application of a single therapy. The severely compromised airways of an adult with cystic fibrosis may not be as responsive to gene therapy as those of an infant or a child.

Although there will continue to be some universal treatments applicable to all of these patients, physicians will increasingly need to decide on which is the best overall therapy regimen for each patient. With the advances in research studying the genotype-phenotype relationship, individual treatments based on a specific patient's mutations and phenotype are on the horizon.[10]

As we enter the next millennium, we will be challenged by important advances in medicine. Some of these advances will have a profound effect on how we treat and view disease. At the heart of these advances will be the research efforts, both laboratory and clinical, concerned with the mechanisms underlying a given disease and the amelioration of this disease. The cystic fibrosis research effort has played a substantial role in helping define the areas that will need to be explored for the development of effective therapy. In particular, the gene therapy effort in cystic fibrosis has provided insight into hurdles that must be overcome to make it an effective alternative or complement to pharmacologic therapies. In their review, Marelich and Cross stress this point and emphasize the need for continued focus on the development of mechanical and pharmacologic therapeutic intervention for the treatment of patients with this disease. Although the potential for gene therapy is great, it is still in its infancy and must go through its growing pains before that potential will be actualized.

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REFERENCES

1. Taussig LM: Cystic fibrosis: An overview. *In* Cystic Fibrosis. New York, NY, Thieme-Stratton, 1984, pp 1-9

2. Anderson DH, Hodges RG: Celiac syndrome—V. Genetics of cystic fibrosis of the pancreas with a consideration of etiology. Am J Dis Child 1946; 72:62-80

3. di Sant'Agnese PA, Darling RC, Perera GA, Shea E: Abnormal electrolytic composition of sweat in cystic fibrosis of the pancreas—Clinical significance and relationship of the disease. Pediatrics 1953; 12:549-563

4. Quinton PM: Chloride impermeability in cystic fibrosis. Nature 1983; 301:421-422

5. Knowles M, Gatzy J, Boucher RC: Increased bioelectric potential differences across respiratory epithelia in cystic fibrosis. N Engl J Med 1981; 305:1489-1495

6. Knowles MR, Stuttes MJ, Spock A, Fischer N, Gatzy JT, Boucher RC: Abnormal ion permeation through cystic fibrosis respiratory epithelium. Science 1983; 221:1067-1070

7. Widdicombe JH, Welsh MJ, Finkbeiner WE: Cystic fibrosis decreases the apical membrane chloride permeability of monolayers cultured from cells of tracheal epithelium. Proc Natl Acad Sci USA 1985; 82:6167-6171

8. Barthelson R, Widdicombe J: Cyclic adenosine monophosphate-dependent kinase in cystic fibrosis tracheal epithelium. J Clin Invest 1987; 80:1799-1802

9. Anguiano A, Oates RD, Amos JA, et al: Congenital bilateral absence of the vas deferens—A primarily genital form of cystic fibrosis. JAMA 1992; 267:1794-1797

10. Gan KH, Veeze HJ, van den Ouweland AM, et al: A cystic fibrosis mutation associated with mild lung disease. N Engl J Med 1995; 333:95-99

11. Yang Y, Li Q, Ertl HCJ, Wilson JM: Cellular and humoral immune responses to viral antigens create barriers to lung-directed gene therapy with recombinant adenoviruses. J Virol 1995; 69:2004

12. Marelich GP, Cross CE: Cystic fibrosis in adults—From researcher to practitioner. West J Med 1996; 164:321-334

13. Tosi MF, Zakem-Cloud H, Demko CA, et al: Cross-sectional and longitudinal studies of naturally occurring antibodies to *Pseudomonas aeruginosa* in cystic fibrosis indicate absence of antibody-mediated protection and decline in opsonic quality after infection. J Infect Dis 1995; 172:453-461

14. Bonfield TL, Panuska JR, Konstan MW, et al: Inflammatory cytokines in cystic fibrosis lungs. Am J Respir Crit Care Med 1995; 152:2111-2118

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Can the Ottawa Ankle Decision Rules Be Applied in the United States?

To the Editor: In the January 1996 issue of The Western Journal of Medicine, Leslie Milne, MD, of San Diego, California, advises us to go by the Ottawa Ankle Decision Rules to avoid taking unnecessary ankle x-rays.[1]

In our community, this is folly. Anyone who has been in practice for a while knows that the reason we take these x-rays is legal, not medical. I am sure the Ottawa Ankle Decision Rules were known to Hippocrates and everyone who followed him. In Canada, the legal system does not have a contingency fee, nor are physicians necessarily subject to the scrutiny of a jury of their "TV-literate, question-oxymoronic" peers on matters that they cannot comprehend.

We live in a nation whose legal system serves by and large, to paraphrase a famous attorney, "a nation of attorneys, by attorneys, and for attorneys" and that has established a legal system whereby lawyers get a share of any action, necessary or not. Anyone who shows up at an emergency department with an ankle complaint darned well better get x-rays, or the physicians will pay if they don't have them taken.

Anyway, what's all the fuss? A $50,000 fluoroscan machine can give a reading in a twinkling. It costs $30,000 to process any single claim, whether anything comes of it or not, according to our malpractice carrier. My advice: Buy a fluoroscan, photograph all symptomatic ankles, take x-rays of them all, and have them documented. Let the Canadians practice medicine under their legal system, and don't try to tell us how to practice it under our legal system.

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REFERENCE

1. Milne L: Ottawa ankle decision rules (Epitomes in Emergency Medicine). West J Med 1996; 164:67

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Dr Milne Responds

To the Editor: My article on the Ottawa ankle rules was merely a summary of the current literature on the subject, not necessarily a recommendation for anyone practicing in a given community. As an emergency physician in California, however, I have found these rules to be helpful. My approach is to explain to patients why I do not think they need a radiograph, particularly if it will not change how I treat them even if there is a small fracture. Then I let them make the choice. I would estimate that they request the film a little less than half the time. I always document on the chart why I did or did not get the radiograph and now refer to the Ottawa rules.

It is my hope that the medical profession is making a greater effort to standardize medical care in a fiscally responsible way in the United States. These ankle rules are a perfect example of a highly sensitive tool that is helpful in safely limiting costs. In our emergency department, I do not order a head computed tomographic scan on every patient with a headache, nor do I radiograph the cervical spine of all motor vehicle accident victims if the results of the history and physical examination do not give me cause for concern. Both of these areas run an even greater liability risk than a missed ankle fracture, but I think I must use some judgment, supported by the literature, in practicing medicine.

Certainly anyone can "sue" for anything anytime, and they do. The question is, "Do they have a legitimate case?" In malpractice claims, plaintiff patients must show that defendant physicians breached the standard of care and that that breach caused an alleged injury. Because the Ottawa Ankle Decision Rules are now considered, at least by some, the standard of care for ankle injuries, proper documentation of why the radiograph was not obtained should stand a physician in good stead in any legal action.

From a financial aspect, health maintenance organizations are relying on standards of care to help them determine which charges should be reimbursed. My guess is that in the not-too-distant future, these agencies will demand documentation of the need for radiographs in simple ankle sprains. Certainly the radiographs are not dangerous, but are they necessary?

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The Role of Hyperbaric Oxygenation Therapy for Necrotizing Fasciitis

To the Editor: The case report on necrotizing fasciitis in the October 1995 issue raises three concerns.[1] First, we are not convinced that the *Vibrio* organism was a pure isolate from the necrotizing fasciitis wound. The presentation of the bacteriologic data suggests that it may be, but is vague enough to leave this question in doubt. More likely, and as is usual, cultures from a specimen of necrotizing fasciitis grow mixed flora. Consequently, we question whether this case can truly be classified as a pure fulminant *Vibrio cholerae* non-O1 necrotizing fasciitis.

Second, the authors considered the patient to be immunocompetent. Although this may be a matter of definition, there is little question in our minds that this patient was a "compromised" host with underlying diabetes mellitus, previous foot operations, previous episodes of cellulitis, and a chronically infected ipsilateral foot wound. Patients with wound infections by non-O1 *V cholerae* frequently have underlying diseases (such as diabetes).[2(p1488)] The importance of this information is that a patient with compromising host factors, presenting as the patient in

this case report did, should be suspected of having a necrotizing soft tissue infection. Surgical intervention at the time of presentation—exploration, decompression, and debridement—may have prevented the ablative operations. The patient's response to interventions was what we would expect from a compromised host—that is, slowly healing wounds, extended antibiotic coverage, and additional operations.

Finally, the authors fail to mention the role and apparently did not consider the use of hyperbaric oxygenation (HBO) therapy as an adjunctive intervention in the management of this patient's necrotizing fasciitis. Reviews indicate mortality rates decrease by 50% when HBO is used as an adjunct.[3,4] Our own experiences have shown similar benefits. Of equal importance, the incidence of major amputations (such as leg, forearm, or entire limb) has almost been totally eliminated when we use HBO as an adjunct to the surgical and medical management of necrotizing fasciitis. In addition, the need for multiple surgical debridements is greatly reduced with the usual situation of only one additional in-operative department debridement after the initial exploration, decompression, and debridement. A third return to the operating department is usually for definitive coverage and closure of the wound. Regardless of the etiologic agent, we recommend HBO be used for necrotizing soft tissue infections, especially in a compromised host.

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REFERENCES

1. Wagner PD, Evans SD, Dunlap J, Ballon-Landa G: Necrotizing fasciitis and septic shock caused by *Vibrio cholerae* acquired in San Diego, California. West J Med 1995; 163:375-377

2. Stein JH (Ed): Other pathogenic vibrios, *In* Internal Medicine, 3rd edition. Boston, Mass, Little, Brown, 1990

3. Hyperbaric Oxygen Therapy—A Committee Report. Bethesda, Md, Undersea and Hyperbaric Medical Society, 1992, UHMS publication No. 30 CR(HBO), pp 38-43

4. Riseman JA, Zamboni WA, Curtis A, Graham DR, Konrad HR, Ross DS: Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridement. Surgery 1990; 108:847-850

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Dr Ballon-Landa Responds

To the Editor: Drs Strauss, Chung, Hart, and Weinstein bring up several interesting points. We wholeheartedly agree that hyperbaric oxygenation (HBO) therapy is a valuable adjunct in the treatment of necrotizing fasciitis caused by any agent and would have been of value in our patient, had it been available. We have previously reported on the use of this modality in such a case, wherein *Aeromonas hydrophila* was the pathogen.[1] Unfortunately, the hyperbaric chamber in our hospital, which was the first one in a civilian hospital in San Diego County, was a casualty of the difficult economic times that have befallen our institutions, and currently HBO is not readily accessible to us or to most of our colleagues.

Bacterial synergism is seen in a majority of cases of this syndrome, and clinicians must diligently look for evidence of mixed infection. We did and found none. The surgical specimens of the necrotic tissue were carefully cultured for aerobes, anaerobes, fungi, and acid-fast bacilli, and the results were a pure culture of non-O1 *Vibrio cholerae*. We expected that we would have recovered other organisms from the necrotic material, as has been our experience, if they were there. Two different laboratories confirmed this organism's identity. This organism seems to have acted alone in the fascial planes.

Our patient had intact cellular and humoral immunity, as measured by the usually available tests. Whereas his immune system was competent, we agree that he was, by virtue of his diabetes, previous infections, and previous operations, a compromised host at increased risk of infections developing.

Everybody agrees that the sooner the diagnosis is suspected, the sooner patients will arrive at surgical debridement and, in turn, the better the chance for salvage. Every experienced clinician also realizes, however, that its recognition can be extremely difficult in the earliest hours, as it was in our patient. Medical science is currently in need of a diagnostic test that will more accurately predict which patients with early absent or equivocal clinical signs will benefit from surgical therapy and which will not.

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REFERENCE

1. Hennessy ALT, Ballon-Landa GR, Jones JW, Farrell T: *Aeromonas hydrophila* gas gangrene: A case report of management with surgery and hyperbaric oxygenation. Orthopedics 1988; 11:289-293

Latino Belief of Alleged Medical Procedure

To the Editor: Various studies have described specific Latino beliefs that may have implications for medical practice, for example *empacho* ("intestinal obstruction"), *mollera caida* ("fallen fontanelle"), *ataques de nervios* ("nervous attack"), and *susto* ("fright," "shock").[1-4] We became aware of the possibility of another highly unusual belief that can affect medical professionals involved in newborn care. It is thought, according to Latino informants, that during the postneonatal examination, physicians perform a procedure that entails "cutting, "opening," or "breaking" the hymens of newborn female infants.

To find out how widespread the belief is, we interviewed 105 Latino (Mexican, Mexican American, Guatemalan, and El Salvadoran) patients and health care professionals at a community clinic in El Cajon, California. Spanish- and English-language question-

naires were used to collect demographics and characteristics of the belief. Of the 105 persons interviewed, 64 had heard of the alleged procedure done on newborn female infants in the United States. Some maintained that the purpose for the procedure is to reduce the pain girls may experience with their first sexual intercourse. Others added that the procedure is done in the United States because girls participate in sexual practices at an early age, and hence the procedure benefits them. A few explained that the procedure was for hygienic purposes—that is, it helps decrease possible female medical problems in the future. Whatever the purpose given, the consequence of the alleged procedure was the same. They believed it resulted in the loss of a highly esteemed cultural value—their daughter's virginity.

Informants first heard of the belief in North America and Central America, including California, Texas, Arizona, Illinois, Mexico, Guatemala, and El Salvador. Our data do not elucidate the origin of the belief, but several hypotheses are proposed. Most of the hypotheses offered are based on the lack of knowledge of female anatomy. For example, many laypeople do not realize that females are born with an opening in the hymen. Furthermore, many tend to confuse the urethra with the vagina. For instance, parents may think physicians insert catheters into the vagina, hence breaking the hymen and robbing the child of her virginity. The parents' unfamiliarity with the postneonatal examination for congenital dislocation of the hip may lead them to think that the hymen is being broken. In addition, the common finding of vaginal blood or mucous discharge in a newborn's diaper may confirm the belief and serve as evidence of a ruptured hymen.

Because male circumcision is not as common in Mexico as in the United States, parents may, because of language barriers, confuse male circumcision with a female procedure. Confusion may also exist because of the historical practice of clitoridectomy in the United States and Europe.[5-7] The possibility of female circumcision existing in South America may have influenced the belief. Although there is no evidence to support the practice of female circumcision in South America, it is claimed to have occurred in Brazil.

The belief may also have emerged and spread as a fear mechanism to control people's movement—for migration or immigration purposes. It may serve as a means to prevent immigrants from crossing the US–Mexico border to give birth in the United States. Another explanation is that the belief may have been encouraged to deter Latinas from leaving their native countries.

The fact that 61% had heard of the alleged procedure and that nine informants claimed to have known someone who underwent it is enough to warrant attention to the need to educate patients and health care professionals. It is essential that both health care professionals and patients be made aware that there is no such medical procedure practiced in the United States. Health care professionals need to be informed of the belief so they can be sensitive to people's concerns, educate parents, and stop the spread of the belief. Latino parents need to be educated and informed of female anatomy, postneonatal medical procedures, and the difficulty of differentiating a virgin from a nonvirgin. If the belief continues to circulate, it may have harmful consequences. Parents may be reluctant to take their young children for physical examinations. Although the data do not reflect the effects the belief may have on seeking medical attention, responses imply that the loss of virginity has strong social ramifications for Latina children and their families. Further studies could elucidate the origins, extent, and implications of this belief.

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REFERENCES

1. Weller SC, Pachter LM, Trotter RT Jr, Baer RD: *Empacho* in four Latino groups: A study of intra- and inter-cultural variation in beliefs. Med Anthropol 1993; 15:109-136

2. Kay MA: Fallen fontanelle: Culture bound or cross-cultural? Med Anthropol 1993; 15:137-156

3. Guarnaccia PJ: *Ataques de nervios* in Puerto Rico: Culture-bound syndrome or popular illness? Med Anthropol 1993; 15:157-170

4. Logan MH: New lines of inquiry on the illness of *susto*. Med Anthropol 1993; 15:189-200

5. Barker-Benfield GJ: Sexual surgery, chap 11, The Horrors of the Half-Known Life. New York, NY, Harper and Row, 1976, pp 120-121

6. Bullough V, Bullough B: Sin, Sickness and Sanity: A History of Sexual Attitudes. New York, NY, New American Library, 1977

7. Cloudsley A: Women of Omdurman: Life, Love and the Cult of Virginity. London, Ethnographica, 1983

Expiry Date Display on Drug Packages

To the Editor: The Food, Drugs, and Cosmetics Act (21 CFR §211.137; Expiration Dating) requires an expiry date on all drugs. Drug use past the expiry date may lead to suboptimal therapeutic effect due to loss of potency,[1-3] patient dissatisfaction, adverse effects from degradation products of some drugs (tetracycline, paraldehyde),[2-4] or a malpractice action. Physicians commonly receive free drug samples from pharmaceutic companies. The Medical Board of California requires physicians to fulfill the same dispensing requirements expected from pharmacists while dispensing samples.[5] It is the physicians' responsibility to check each sample's expiry date to avoid inadvertently dispensing an outdated drug.

In the process of discarding outdated drugs, I reviewed the expiry date display on all drugs (n = 20) stored on two shelves of a six-shelf medicine cabinet in a medical office (Royal Medical Group, Santa Ana, California). Each package was checked for whether the expiry date display was embossed or printed, its legibility (type size), and the surface on which it appeared.

Of 20 drug samples studied, the expiry date was embossed in 13 (65%) and printed in 7 (35%) (Table 1). In two samples (10%), part of the expiry date could not be read; in eight samples (40%), the expiry date type was too small and not easily legible. The expiry date appeared on the package side in eight (40%), the bottom in eight (40%), and the rear and the front in one drug each (5%). On two products, the date was displayed only on the contents (not on package surface): Maxzide (hydrochlorothiazide and triamterene) through a window in the package, and Nizoral (ketoconazole) shampoo required opening the package. The date display legibility was good when it was printed in ink and poor when embossed. It could be located easily when it appeared on the package's front, but required searching (turning the package from side to side) when the expiry date appeared elsewhere.

Discussion

The current practice of displaying the expiry date on drug packages is not standardized. The date may be variably embossed or printed and may appear on any surface. Its type size may be too small to read, and part of it may not be legible because of light ink or embossment. For primary care physicians who daily dispense several samples to 20 to 30 patients, it can be cumbersome and time-consuming to check the expiry date. As a result, many physicians do not dispense samples, and many samples become outdated in storage.

I recommend that the expiry date should be universally displayed at a standardized location. Because physicians always read the drug's name, the date should ideally be placed underneath the name on the package's front. It should appear both on outside packaging (eliminating the need to open the package to read the expiry date) and on the inside contents (as it is possible for the loose contents to separate from the package). Because many physicians are past middle age, the type should be of sufficient size to be readable by those with presbyopia (pica type: 10 characters per inch). These suggestions will enhance physician dispensing of drug samples, improve patient care, reduce waste (unused expired samples), and decrease medical care cost (samples are free).

Acknowledgment

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REFERENCES

1. United States Pharmacopeia—The National Formulary, 22nd edition. Rockville, Md, US Pharmacopeial Convention, 1990, pp 1702-1705

2. Sande M, Mandell G: Antimicrobial agents: Tetracyclines, *In* Goodman G, Rall T, Niles A, Taylor P (Eds): Goodman and Gilman's Pharmacologic Basis of Therapeutics, 8th edition. New York, NY, Pergamon Press, 1990, p 1122

3. Hadeler F: Should expiration dates be required on patients' prescription labels? Am Pharm 1986; NS26:30-35

4. Brown JL, Brown NP: Pharmaceutical expiration dating advice given by retail pharmacists. J Am Board Fam Pract 1991; 4:407-410

5. Medical Board of California. Legal Requirements for Distribution of Drug Samples—Action Report, 1996; 56:3

TABLE 1.—*Characteristics of the Expiry Date Display on Drug Sample Packages*

Brand Name (Drug), Lot, Manufacturer	*Expiry Date*	*Package*		
		Nature	*Legibility*	*Surface*
Advil, (ibuprofen),G149, Whitehall	12/96	Printed	Good	Rear
Aerobid, (flunisolide), 921128, Forest	8/94	Embossed	Good	Bottom
Benadryl, (diphenhydramine HCl), 00144B, Parke-Davis	4/96	Embossed	Good	Bottom
Brethaire, (terbutaline sulfate), 1930634, Ciba-Geigy	5/95	Embossed	Poor	Bottom
Cataflam, (diclofenac potassium), 1T002877, Ciba-Geigy	3/95	Printed	Poor	Bottom
Citrucel, (methylcellulose), 1U480D, Lakeside	8/94	Embossed	Good	Front
Desyrel, (trazodone HCl), MAE 38, Mead Johnson	2/95	Embossed	Poor	Bottom
Dimetapp, (combination cold product), 92606, Robins Consumer	6/94	Embossed	Good	Side
Lotensin, (benazepril HCl), 3B010036, Ciba-Geigy	10/94	Embossed	Poor	Side
Maxzide, (hydrochlorothiazide and triamterene), 326-312P, Lederle	2/95	Printed	Good	Inside
Nizoral, (ketoconazole), 93315/091, Janssen	2/95	Printed	Good	Inside
Ocuflox, (ofloxacin), 7?41X,* Allergan	9/95	Embossed	Good	Bottom
Ogen, (estropipate), 72-388-AFA, Abbott	2/95	Printed	Good	Side
Provera, (medroxyprogesterone acetate), 162JY, Upjohn	2/98	Embossed	Poor	Bottom
Robitussin, (guaifenesin), 2?01,* Robins	11/95	Embossed	Poor	Side
Sectral, (acebutolol), 9930104, Wyeth-Ayerst	2/96	Embossed	Good	Bottom
Tavist, (clemastine fumarate), 140U3993, Sandoz	7/95	Printed	Good	Side
Ziac, (bisoprolol fumarate, hydrochlorothiazide), 362-342, Lederle	1/95	Embossed	Poor	Side
Zoloft, (sertraline HCl), A663A, Roerig	1/95	Printed	Good	Side
Zovirax, (acyclovir), 4P1786, Burroughs Wellcome	5/96	Embossed	Poor	Side

HCl = hydrochloride

*Lot number illegible.

Lessons From the Practice

Notes of a Hospice Physician
Journal Entries of January 23 and February 2, 1994

IRA R. BYOCK, MD, *Missoula, Montana*

January 23, 1994

I met Jacob Edwards today. He is 43 and dying of AIDS.

I first heard about Jake from Francis Flowers of the Intravenous (IV) Infusion Service. She stopped me in the parking lot two weeks ago and told me she'd been encouraging Jake and his mom to call. She hoped I would get a chance to meet them and, possibly, be of some help. He was admitted to the hospice a few days later, and two days ago, I was asked by his hospice nurse to see him. Bob Thomas, MD, his internist, enthusiastically agreed.

The staff of IV Infusion Service and the hospice all like Jake and are a bit protective of him, but he has clearly been identified as a "problem patient." He has been in nearly constant struggles with care providers, including Dr Thomas, who is among the most caring and nonjudgmental doctors in town.

Jake acquired the human immunodeficiency virus in a distant city, but has come home to die. He is living in the home of his mother, who is providing his primary care. She seems consistently loving and notably tolerant. Their relationship in the past was stormy at times, and there is still the occasional "gale." Jake is the only son in a family with five daughters. He left home for the California coast as a teenager and became an accomplished musician. He also lived a hard, fast life that included years of polydrug use. He married, but the marriage succumbed to the drug abuse. Jake says he and his wife still love each other. They have two daughters, a preteen who lives with his wife and another who is off at college. Jake hasn't seen his wife or either of his daughters in the past six years.

During my visit today, Jake lay on his bed, the radio tuned to a commercial rock and roll station. He was alert and oriented, but his affect and expression were somewhat blunted, and there were flashes of irony and anger in the tone of his story. He smoked constantly, alternating between cigarettes and marijuana. He seemed hardly strong enough to do anything else. Even lifting his head to sip water required concentrated effort.

Jake has had a miserable few days of nausea and vomiting. He said he felt better today, though he is clearly dehydrated. He complained only of a mild headache and of generalized weakness. He expressed anger at Dr Thomas and at the health care system. He blames a lot of his problems on the medications he has been given. He has already been through the entire alphabet of antiviral drugs, and, in Jake's mind, the most recent one, ganciclovir, is the cause of all his current problems. He is angry that it was ever prescribed and believes that the herbal medicine he is taking now is a better treatment for the deteriorating vision in his left eye.

Jake clearly knows what a hospice is. He knows that AIDS is ultimately fatal and has seen others die of it. But he isn't focused on dying. He told me he is "going to kick this thing"—at least in the short run. During the visit, we agreed to focus on Jake's primary goal of getting stronger. I said it was realistic to hope that he would gain a bit of strength. Jointly, we arrived at a plan for him to drink as much electrolyte solution as he comfortably could over the next 24 hours, and, as he requested, I arranged for him to receive a liter of saline solution IV tomorrow.

After getting acquainted and attending to the medical aspects of things, I listened to more of Jake's story. We spoke of his daughters, and I was struck by how important they still are to him, despite the years of separation. I asked him if there would be anything left undone if, unexpectedly, he were to die suddenly today, as any of us could. He responded that he needed to make out a will; he told me about the few things he would want to give to specific people in his life. I asked if there were stories, perhaps from his childhood or stories of his life as a musician, that he would want to share with his daughters. Was there anything special he would want them to know? Some bit of wisdom he would want to share with them? Had he written to say how much he loved them? Would he want to write and say good-bye? Would he perhaps be interested in tape-recording some of his stories and saying some of these things? He said that he would.

February 2, 1994

I visited Jake Edwards again today, ten days after meeting him for the first time. There has been a remarkable transformation for this patient and for his family. The family has not always been close and warm, but the at-

(Byock IR: Notes of a hospice physician—Journal entries of January 23 and February 2, 1994. West J Med 1996; 164:367-368)

From the Palliative Care Service, Missoula, Montana.
Reprint requests to Ira R. Byock, MD, Palliative Care Service, 341 University Ave, Missoula, MT 59801.

mosphere in the home today would thaw the coldest cynic. Jake's eldest sister has flown in to be with him, joining his mother and the two sisters who live locally. His older daughter, Julie, is also here, and his wife and younger daughter are expected to arrive by bus this evening. His mom continues to give meticulous, loving care, but with more hands to help, she's finally getting some rest. Everybody is pampering Jake, though they are also taking care to give him his privacy.

Jake's condition has deteriorated notably. He is weak and lethargic and no longer tracking all of the time. When he is alert, he is almost always oriented. He knows well that he is dying.

His daughter Julie already has become fully involved in his care. She clearly loves him, recognizes his failings, and understands the importance of what is happening. Jake remains intermittently cantankerous, but is making a real effort to be tolerant and accepting of the loving care he is receiving. "Jacob is putting up with our fussing," one of his sisters said. The women of this house know he has his limits and are respecting them.

Jake's sister Sue Ann smiled as she related an incident from a recent evening. She had walked into Jake's room and touched the skin of his arms, which were folded across his chest. He felt cool. She asked him if he was cold, and he said, "No." Nevertheless, she tucked his blankets up above his shoulders. He frowned and closed his eyes, but when she asked him if he wanted her to uncover him, he said, "No, I'm all right." She then laid down on the cot at the foot of his bed to go to sleep. A few minutes later, their mother came in and, noticing his arms lying across his chest, asked him if he was cold. He said, "No," and weakly lifted his arms, knowing she was going to cover him anyway. She did. Ten minutes later, out of curiosity, Sue Ann lifted her head to see. Sure enough, his arms were back out from under the blankets.

When another of Jake's sisters describes their care as "doting," all chuckle in agreement. They said Jake's tolerance of their doting feels like a gift he is giving to them. He tolerates the caresses and appreciates the spoonfuls of pudding and the cool water they offer. He is still listening to rock and roll, but expresses some interest in the more tranquil, "New Age" music they suggest.

The ambiance in the home is an improbable mixture of solemnity and celebration. I have seen it often before. It is something like the atmosphere in the homes of mourners: sadness suffused with humor and appreciation for the person departed. It is much like times of "sitting *shiva*" among the Jews.

The gathering of the family and the loving atmosphere in the home are the results of conscious efforts and hours and hours of work. Dr Thomas remains involved and supportive. Jake's symptoms are being managed carefully, ensuring his comfort despite advancing weakness and debilitation. The hospice nurse, social worker, chaplain, aides, volunteers, and I have participated in a host of simple, yet delicate, clinical interventions: Listening, mostly; respectfully exploring relationships without prying; and gently encouraging Jake to reach out to others, even those at a great distance. The hardest and most courageous work, of course, has been done—is being done—by Jake, his mom, his sisters, and his daughter.

How can I explain this transformation to others? How will I tell this story?

Lessons From the Practice

The Road Not Taken

KIRSTI A. DYER, MD, MS, *Santa Barbara, California*

I'm late—almost a month."

This simple statement can elicit a wide range of emotional reactions in women, from elation to apprehension to severe despondency.

The patient was a 19-year-old Chinese foreign student. She had come to the college's student health center for evaluation of a late menstrual period. She was quiet, shy, reserved, and cautious in revealing her history. I could not tell how much she understood of what I was asking or whether she knew the anatomic or sexual terms in her own language, let alone in English. Was the communication problem we were having simply the language difference, or was it also a cultural barrier? Was I asking questions that she was unable to answer out of fear or of ignorance? After some coaxing, she admitted to having genital contact only; there had been no penetration. They had not used any contraceptives.

As part of the evaluation, but more because of an uneasy feeling, I special-ordered a serum pregnancy test. The results would be back within an hour. Sensing her apprehension, I scheduled a second visit for a Pap smear and pelvic examination to give her time to adjust to the idea. It would be her first examination. The test results returned, confirming my intuition. She was pregnant.

I took the patient to a private room to tell her the results. I hoped I could find the right words. It was reminiscent of telling a patient of a cancer diagnosis. Her face went blank, hearing nothing after the words "You are pregnant." She registered only shock. Calmly I repeated myself. "The test is positive. You are pregnant." Her face started to register some vague awareness. I told her she had several options. If she wanted to keep the pregnancy, then I would refer her to an outside obstetrician to assume her care. She could also talk to someone about adoption. If she chose to terminate the pregnancy, then I would refer her to a physician who provided this service.

Her shock dissolved into a full realization of the news, and she began to cry. I pulled her head down to my shoulder and let the tears flow. She was far away from home in a foreign country. Before her now was the monumental decision of what to do with an unplanned pregnancy. She probably had little knowledge about fertility or reproduction, so had not counted on the limited sexual contact causing her to conceive, or she may have been unable to tell me what had really happened. I found a box of tissues and helped dry her tears. After a few minutes of considering her choices, she said, "I don't want to keep it." I again told her of the options and that we could refer her appropriately. She was petrified of being examined by a man, but all of the local physicians who provided these services were male.

We discussed how difficult it must be to face this decision, given her conservative background. She wanted to know if her parents had to be told. I told her that in this country she was considered an adult and that she could decide whether to tell her parents. Perhaps it might be better if they did not know.

Sitting with her as a physician discussing her options and providing her solace for the situation she now encountered, I turned the tables to empathize with her situation. A rush of memories about my own choices came back to me. My decision to deal with an unexpected pregnancy had only ever been a theoretical one. I had asked the "what if?" question during frantic days waiting for a late cycle to start. I had planned on going to college and, once in college, decided on medical school, as did the man I was dating at the time. (We are both physicians now, but long since parted.) Children were not in the picture. My choice was my career. Had I had a child at 19 years, I doubt that I could ever have become a physician. Our paths would not have crossed. I would not have been there to provide this patient reassurance in her time of crisis.

Looking at the road not taken, I realized that I could now have had a teenaged child, have been divorced, and have been just trying to exist. Several of my high school classmates took this route; many are now envious of my career. I am grateful for the road I chose. I do believe, for the sake of my patients—those whom I have kept alive and those whose lives I have touched—that I made the right decision at the time to pursue a career in medicine and not to have a family, although lately I am beginning to wonder, was this price too high? I envy my male colleagues who do not have to make this choice.

Had our paths never crossed, my patient may have seen a physician without my intuition and continued longer unaware of her pregnancy. As it happened, she still

(Dyer KA: The road not taken. West J Med 1996; 164:369-370)

From Cottage Hospital, Department of Internal Medicine, Santa Barbara, California.
Reprint requests to Kirsti A. Dyer, MD, 3754 San Remo #24, Santa Barbara, CA 93105.

had time and options. The choice was hers to make. I do not know her final decision. She did not return to the clinic during the time I was there.

But the shocked look on her face still haunts me. I wish that the news had been different. Mostly, I wish that I could have done something more to ease her pain and distress.

I consider myself fortunate that such a decision has never been mine to make. I do know what my answer would have been, faced with the same choice. Parenthood was the road I could not take.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press 1966, pp 35-51 [author of book is same as author of chapter]

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Edition. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 [authors of book differ from chapter author]

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intraarterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications **(Do not include in reference list; put in text)**

(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee,* September 8, 1985, p 5)

Personal Communications and Unpublished Data

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

ABSTRACTS APRIL 1996

(Barrie W: Cost-effective therapy for hypertension. West J Med 1996; 164: 303-309)

The costs of treating hypertension are out of control. The Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure and others recommend the use of diuretics and β-blockers as first-line agents. Newer drugs such as calcium channel blockers, α-blockers, and angiotensin-converting-enzyme inhibitors have improved metabolic profiles, but have not been proved in long-term, randomized, controlled trials to reduce morbidity and mortality. Our General Medicine Clinic has gradually shifted toward prescribing the newer agents. We reviewed our drug use, evaluated the literature, and made recommendations in the form of guidelines. Clinicians' concerns included quality-of-life issues, sexual dysfunction, metabolic changes—lipids, potassium, insulin resistance—and others. These concerns were addressed, and a consensus was reached. Our goal is to streamline therapy, reduce costs, and provide proven effective medication.

HYPERTENSION **ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS**

(Barrie W: Cost-effective therapy for hypertension. West J Med 1996; 164: 303-309)

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January 1996

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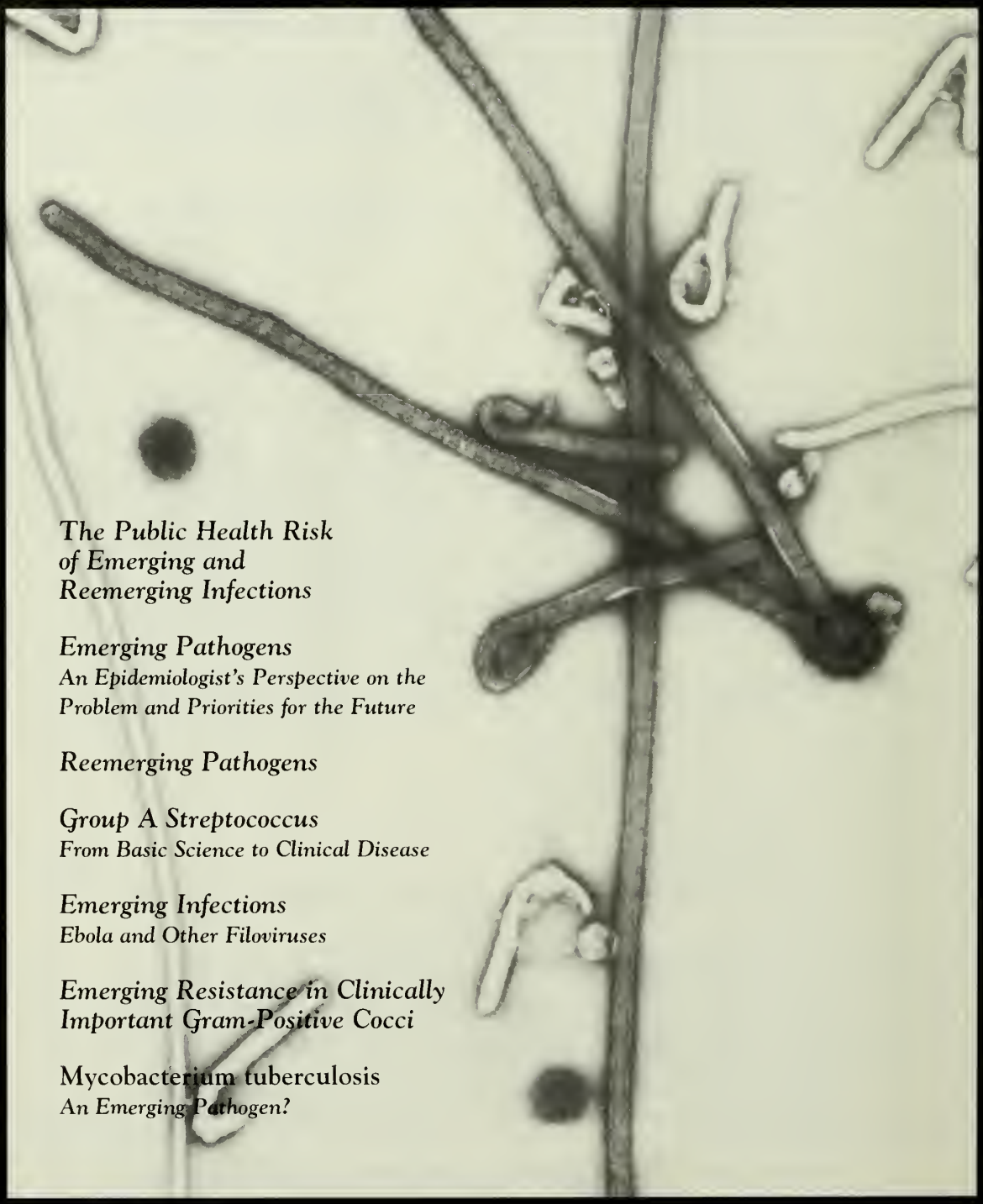
GLOBAL MICROBIAL THREATS



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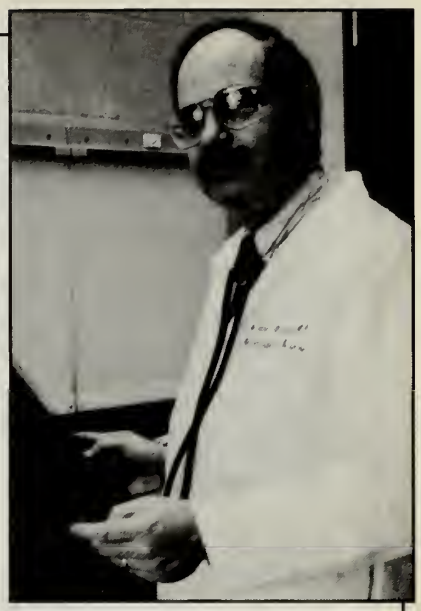

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Busy 4-person family practice clinic seeking 5th doctor.

University of Washington-affiliated. Looking for BE/BC family practice physician interested in providing excellent medical care and teaching WAMI program medical students/residents. Accredited hospital in beautiful Southeast Alaska. Fee for service practice with sensible patient load. Comprehensive benefits. Negotiable salary. Stable community with wide variety of activities and opportunities located on Inland Passage. Send CV to Bill Henrickson, MD, Ketchikan Medical Clinic, 3612 Tongass Avenue, Ketchikan, AK 99901; or call (907) 225-5144. Fax (907) 247-0920. Not J-1 position.

FAMILY PHYSICIAN WANTED. Seattle community health center serving Asian and Pacific Islander immigrant population is expanding its services. Need a full-time family physician to include OB. Bilingual skills a plus. Contact Donna Taylor at (206) 461-3617 or send CV to 675 S Lane St, Ste 303, Seattle, WA 98104.

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Call Pat Lam, 10 am-10 pm PST: 1-800-258-4526.

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Our program offers a professionally stimulating environment, a quality lifestyle in the Pacific Northwest and a competitive salary/benefits package. **Forward inquiry and C.V. to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah Street, Suite 100, Portland, OR 97232-2099. EOE.**

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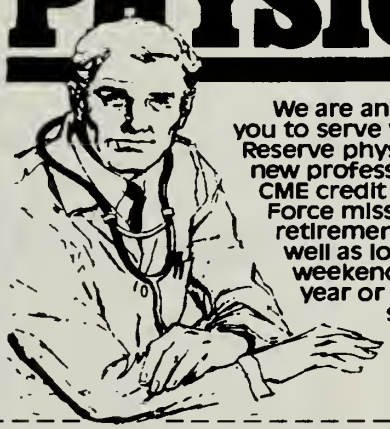

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Outpatient HIV clinic in Santa Fe, New Mexico has immediate need for locum tenens physician. Position requires knowledge of current drug therapies, and the latest advancements in the care and treatment of people living with HIV/AIDS. Background in infectious diseases a plus. May lead to regular full-time position.

The AIDS Wellness Program (AWP) was established in 1988 and serves approximately 280 clients with HIV/AIDS. The clinic is a division of VNS Health Services, Inc. established in 1962. VNS is a non-profit organization dedicated to community medical services throughout northern New Mexico.

For more information, please contact Kit Machin, Director of Human Resources at (505) 984-0103, ext 247, or send a CV to VNS Health Services, Inc., 811 St Michael's Dr, Santa Fe, NM 87505. EOE/Drug-free workplace.

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FULL-SCOPE FAMILY PHYSICIAN needed at La Clinica de la Raza, a progressive non-profit community health center & NHSC loan repayment site in the San Francisco Bay Area. Current California license, family practice, BC/BE, current DEA. Bilingual English/Spanish or Cantonese preferred. Salary with extra pay for hospital work. Excellent fringe benefits. Send CV to: Patricia Royball, Personnel Manager, La Clinica de la Raza, 1515 Fruitvale, Oakland, CA 94601. (510) 535-4090. EOE

WASHINGTON STATE—Rapidly growing semi-rural primary care clinic needs BC/BE FP to join four others. Full facilities, strong IPA, quality motivated staff. Close to Mt. Rainier, Puget Sound, urban areas. CV to W.N. Elledge, MD, Box 760, Yelm, WA 98597; FAX (360) 458-6612.

Be contemplative like this desert big horn sheep. Think over your choices of lifestyle.

An office for an otolaryngologist is available. The office is well-equipped with a good microscope and complete audiological facilities, including a spacious sound-treated room and audiometers. This is a pleasant, small college town in the Utah desert. It offers many outdoor activities, including mountain biking, cross-country skiing, fishing, and big-game hunting. In two hours you can reach premier skiing resorts including Alta and Snowbird. The office is next to a top-rated Columbia-HCA hospital. The hospital will reimburse you and your spouse for travel expenses if you visit to look it over. Call David Hilding, MD at (801) 637-4327 or write 945 W Hospital Dr, Price, UT 84501.

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SANTA FE, SANTA FE. 2 FP's need board-certified Family Practitioner to join women's health practice. Obstetrics required. Innovative practice with interest in traditional and alternative therapies. Job sharing OK. Call (505) 983-3837, FAX (505) 820-2733.

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✗ For more information and details, please contact: David Hoeft, MD, Wilson Clinic, 212 Carlanna Ave, Ste 100, Ketchikan, AK 99901. Phone: (907) 225-4104; FAX: (907) 225-7215; or Ed Mann, (907) 225-5171, x389.

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LARGE NORTHERN CALIFORNIA MULTISPECIALTY group with national reputation for excellence, seeks recently trained BC pediatrician. An exciting position for energetic, creative person to become integral part of innovative managed-care team. Competitive experience-based salary. Excellent benefits. Forward letter detailing professional interests, goals, CV to Box 311, *The Western Journal of Medicine*, PO Box 7602, San Francisco, CA 94120-7602.

CALIFORNIA—EMERGENCY MEDICINE/FAMILY PRACTICE. California Emergency Physicians Medical Group is a partnership of Emergency Medicine and ambulatory care specialists contracting with over 30 Emergency Departments and 10 ambulatory care centers in Northern, Central, and Southern California. We are seeking BC/BP Emergency Medicine and Family Practice Physicians. We offer attractive compensation, ownership, health, disability, and retirement benefits. Send your CV or contact John Gravette, CEP, 2101 Webster St, Ste 1050, Oakland, CA 94612; (800) 842-2619.

PEDIATRIC CLINIC OPPORTUNITIES—Full-time and part-time opportunities are available in locations throughout the western United States. Established patient base. Equipment as well as complete scheduling and billing provided. We offer competitive remuneration and occurrence malpractice insurance. Contact Rod Thirion or Ev Walters at (800) 288-8044 or FAX your CV to (719) 598-7945.

THE UCSF/MOUNT ZION OCCUPATIONAL MEDICINE CLINIC is seeking two physicians to fill two 50-100% Associate Physician openings. The primary duties are clinical, including injury and illness care, medical surveillance, disability, fitness for duty, and preplacement examinations. The incumbent will educate employees on safe work practices, self care, and health promotion. The successful candidate will have experience in providing urgent care and workers' compensation care, a current California medical license, and excellent communication skills. Board eligibility or certification in internal medicine, emergency care, or occupational medicine preferred. Submit a CV to UCSF, Dept of Human Resources, 1350 7th Ave, San Francisco, CA 94122. UCSF is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

PREVENTIVE MEDICINE, COMMUNITY-ORIENTED MEDICINE TRACK. Inviting application to the University of California-San Diego State University General Preventive Medicine Residency Program from applicants interested in community-oriented preventive medicine training. Training will be conducted in multicultural, medically underserved areas. Physicians with an interest in community-oriented medicine and who have primary care experience are encouraged to apply. Salary $34,000 with full benefit package. Call Netta Glover (619) 594-5332. Write: UCSD-SDSU General Preventive Medicine Residency, San Diego State University, 5500 Campanile Drive, San Diego, CA 92182-4701. Fax (619) 594-5613. E-mail: glover@mail.sdsu.edu.

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We are seeking an experienced medical director for a large, stand-alone urgent care center in Las Vegas, NV. This urgent care center sees 200 patients daily, has a high acuity rate, 23-hour observation unit, and lab and radiology resources on site. Successful candidates will be BC/EM, FP, or IM with both EM and management experience.

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PRIMARY CARE INTERNIST—THE EVERETT CLINIC, a 135-physician multispecialty group, is seeking BC/BE internist to associate with 17-person department. Position located at a new satellite office. The main clinic is 25 miles north of Seattle and has 5 rapidly expanding satellite offices. Opportunity for exceptional personal/professional lifestyle. Position offers competitive salary with excellent benefits. Available October 1996. Send CV to J.G. Finley, MD, The Everett Clinic, 3901 Hoyt Avenue, Everett, WA 98201.

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OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 18 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (503) 482-4951. No J-1 Opp.

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PRIMARY CARE PHYSICIAN (INTERNIST/FAMILY PRACTITIONER) needed to join a primary care/multispecialty medical group in San Diego. Competitive salary. Please fax CV to (619) 270-1864. If any questions, call (619) 272-0170, 9-5:30 weekdays.

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EXCELLENT OPPORTUNITY for BE/BC general internist to join a 76-physician multispecialty clinic in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. New internist joining the clinic will quickly become busy as two of the internists in the group will retire during 1996.

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June 22, 1996

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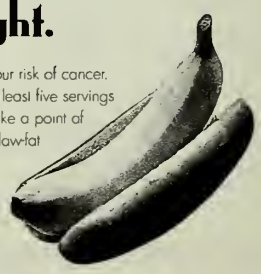

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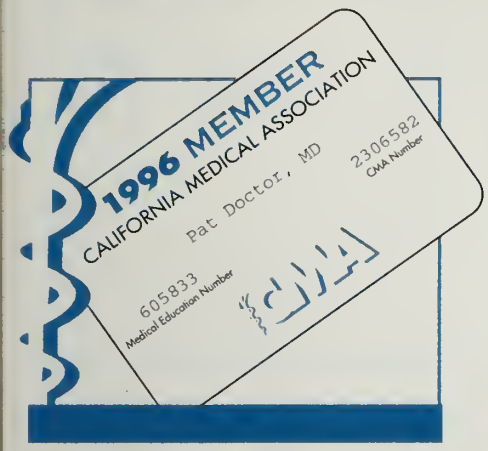

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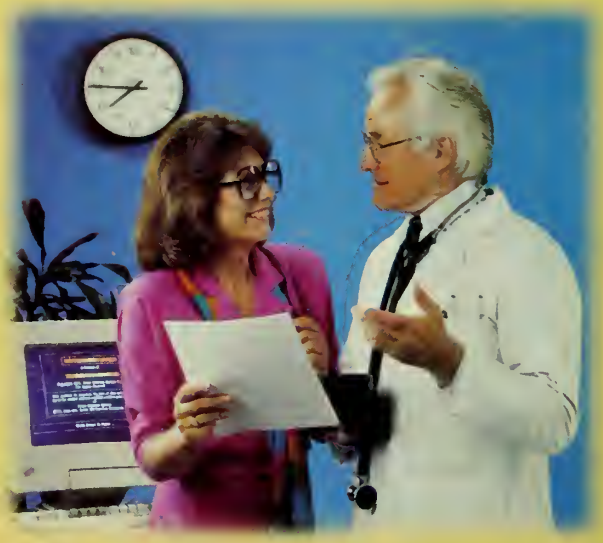

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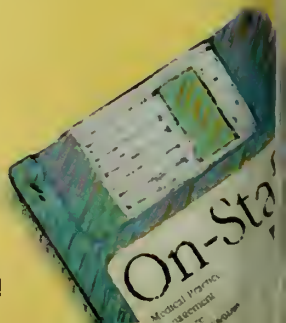

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Manuscripts for consideration should be sent to the editor, Linda Hawes Clever, MD, PO Box 7602, San Francisco, CA 94120-7602; overnight mail, 221 Main St, San Francisco, CA 94105.

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What has CMA done for you lately...

PROTECTING PHYSICIANS

The New **CMA**

MEDICAL BOARD OF CALIFORNIA

PROTECTING PHYSICIANS

CMA obtained modifications of MBC public disclosure policy to appropriately protect physicians' right to privacy and opposed a licensing fee increase.

- Obtained a preliminary injunction prohibiting MBC from disclosing pre-accusation investigatory information.
- Succeeded in getting MBC to modify its public disclosure policy to address CMA's major concerns.
- Urged the California Supreme Court to review two cases in which the appellate courts had ruled that MBC may access confidential peer review records. The Supreme Court agreed suggesting that the Court is sympathetic to CMA's view that the law bars MBC from reviewing confidential medical staff records.
- When California Physicians were at their breaking point regarding licensing fee increases, CMA single handedly persuaded MBC to retract its proposed $100 fee increase.

PROFESSIONAL LIABILITY

PROTECTING MICRA

The fact that California's malpractice rates are among the lowest in the nation is no accident. Since 1975, when CMA's hard-fought MICRA tort reform was enacted, there has not been a single change. Much credit goes to CMA's attorneys, who monitored all cases involving MICRA and physician's rights in professional liability cases.

- Successfully eliminated, as precedent, a case which would have allowed plaintiffs attorneys to make claims for lost "chance of survival," even when it is more likely than not that physician's alleged negligence had caused harm.

REIMBURSEMENT ASSISTANCE

HELPING PHYSICIANS WITH SPECIFIC PROBLEMS

CMA continued to help many individual members correct payment problems with various carriers and health plans throughout the state. As a result of CMA action, Blue Shield rescinded its request for refunds of payments for claims from about 4,600 physicians. CMA also helped physicians receive refunds from a company that unfairly charged fees to physicians' credit cards.

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SOUTHERN MEDICAL ASSOCIATION

SUMMER 1996 EDUCATIONAL CALENDAR

CME CONFERENCES

20th Annual Lung Symposium
The Cloister, Sea Island, GA
June 9-13, 1996

Global Management of Work-Related Musculoskeletal Injuries
Ritz-Carlton-Naples, Naples, FL
June 14-16, 1996

Cancer Strategies for the Practicing Physician
The Cloister, Sea Island, GA
July 22-24, 1996

7th Annual Focus on the Female Patient
Kiawah Island Resort, Kiawah Island, SC
July 22-25, 1996

5th Annual General Surgery Update
The Cloister, Sea Island, GA
July 26-28, 1996

4th Annual Primary Care Update: What's New in Dermatology
Kiawah Island Resort, Kiawah Island, SC
July 26-28, 1996

Sports Medicine & Soccer Symposium
The Parliament House, Birmingham, AL
July 26-28, 1996

Advanced Orthopaedic Imaging
The Cloister, Sea Island, GA
July 29-August 1, 1996

Pain Management in the Office Setting
The Cloister, Sea Island, GA
August 2-4, 1996

Advances in Geriatric Medicine
Lago Mar Resort & Club, Ft. Lauderdale, FL
August 9-11, 1996

Gastroenterology Update for Primary Care
Marriott's Bay Point Resort, Panama City, FL
August 16-18, 1996

Common Clinical & Practice Skills: Use & Interpretation
Ritz-Carlton-Palm Beach, Manalapan, FL
August 23-25, 1996

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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- Developed our own medical-loss ratio survey after sponsored legislation was vetoed by the Governor.

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A great success story in 1995, CMA developed California Advantage, Inc. that now has more than 6,500 shareholders and is on track to enter the marketplace on July 1, 1996, with a statewide PPO and EPO offered through the Health Insurance Plan of California.

INSTITUTE FOR MEDICAL QUALITY

QUALITY HEALTH CARE

As part of CMA's reorganization and its commitment to taking the lead role in shaping the future of health care in California, we are creating a new subsidiary, the Institute for Medical Quality. Initially, it will house CMA's existing quality assurance and accreditation programs. In the future, we plan to develop new accreditation programs relating to quality evaluation of HMOs and integrated health care systems, as well as accreditation of physician offices.

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

August 5-10—**1996 Comprehensive Internal Medicine Board Preparation Course.** Marriott's Camelback Inn, Scottsdale. Mon-Sat. Contact: Beverlee Anderson, (602) 267-5366.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

August 2-4—**A Midsummer Night's Wheeze.** American College of Allergy, Asthma and Immunology at La Costa Resort & Spa, Carlsbad. Fri-Sun. 8 hrs. $110-$195. Contact: California Society of Allergy and Clinical Immunology, (714) 828-8022.

CARDIOLOGY

June 1—**2nd Annual UCSD Heart Failure Symposium.** UCSD at Sheraton Grande Torrey Pines. Sat. 6.5 hrs. $40. Contact: UCSD, Barry Greenberg, (610) 543-7751.

June 5-8—**Advanced Echocardiography and Doppler Ultrasound 1996.** American College of Cardiology at Hyatt Islandia, San Diego. Wed-Sat. 23.5 hrs. Contact: ACC, Registration Secretary, Extramural Programs Dept, Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

June 28-30—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt Fisherman's Wharf, San Francisco. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421- 3756.

DERMATOLOGY

June 7-9—**3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery**. UCSF at UCSF. Fri-Sun. Contact: UCSF.

October 5-9—**11th Combined Skin Pathology Course & Workshop in Dermatopathology.** UCSD at San Diego Princess. Sat-Wed. 37 hrs. $600. Contact: UCSD.

October 12-13—**The Skin From A To Z: Tips on Practical and Office Techniques.** UCSF at UCSF. Sat-Sun. Contact: UCSF.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 2-3—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSD at San Francisco. Sat-Sun. Contact: UCSD.

EMERGENCY MEDICINE

June 17-21—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

June 20—**Cost Effective Emergency Medicine.** American College of Emergency Physicians at The Mirage, Las Vegas. Thurs. 8 hrs. $199-$249. Contact: Alpen Meeting Services, (800) 451-RISK.

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency La Jolla, San Diego. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

October 20-23—**Cellular Injury and Brain Edema, 1996.** Foundation for Pediatric and Laser Neurosurgery, Inc. at Hyatt Regency Hotel, San Diego. Sun-Wed. 19 hrs, $350-$400. Contact: Hector E. James, MD, Coordinator, Foundation for Pediatric and Laser Neurosurgery, Inc, 7930 Frost St, Ste 304, San Diego 92123. (619) 560-4791.

October 21-25—**Emergency Medicine Symposium I.** UCSD at San Diego. Mon-Fri. 32 hrs. $495. Contact: UCSD.

November 11-15—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

December 16-20—**Emergency Medicine Symposium II.** UCSD at UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

June 7-11—**Molecular Steriodogenesis.** UCSF at Monterey. Fri-Tues. $300. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

June 6-7—**10th Annual AIDS Update for Primary Care**. Alta Bates Medical Center at Mills College, Oakland. Thurs-Fri. 7 hrs. $200. Contact: Medical Education Dept, Alta Bates Medical Center, 2450 Ashby Ave, Berkeley 94705. (510) 204-3884.

June 7-9—**9th Annual Medical Office Laboratory Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego. Fri-Sun. 23 hrs. $475. Contact: Nancy Geiser, College of Extended Studies, (619) 594-6255.

June 9-14—**20th Annual Fingers to Toes Primary Care Orthopaedics.** UC Davis at Fallen Leaf Lake, Lake Tahoe. Sun-Fri. 26 hrs. $495-$540. Contact: UCD.

June 10-12—**2nd Annual Sports and Occupational Medicine in Primary Care: From Prevention to Treatment Conference.** San Diego State University Health Services at Red Lion Hotel, San Diego. Mon-Wed. 20 hrs. $475. Contact: Nancy Geiser, College of Extended Studies, (619) 594-6255.

June 12-22—**A Week in Family Practice: American Board of Family Practice Specialty Board Review Program.** Finch University of Health Sciences at Red Lion Hotel, Costa Mesa. Wed-Sat. 67.5 hrs. $1,050. Contact: (800) 533-8850.

June 28-30—**San Diego Academy of Family Physicians' 40th Annual Postgraduate Symposium—Family Medicine Update: 1996.** San Diego Academy of Family Physicians at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $225-$300. Contact: Terry Camarata, (619) 422-1186.

July 8-11—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $425-$475. Contact: UCSF.

August 2-4—**Managing Respiratory Diseases.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

August 2-4—**Cardiology for the Primary Care Physician.** Continuing Medical Education Associates at Hotel del Coronado, Coronado. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 5-7—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, Coronado. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Doubletree Hotel, Monterey. Fri-Mon. 11 hrs. $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

October 9-12—**Semiannual Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

GERIATRICS

June 7-8—**Geriatrics: Caring for the Older Patient in a Managed Care Environment.** UC Davis at Sacramento Hilton Inn. Fri-Sat. 12 hrs. $185. Contact: UCD.

INFECTIOUS DISEASE

June 6-7—**10th Annual AIDS Update for Primary Care.** Alta Bates Medical Center at Mills College, Oakland. Thurs-Fri. 7 hrs. $200. Contact: Medical Education Dept, Alta Bates Medical Center, 2450 Ashby Ave, Berkeley 94705. (510) 204-3884.

October 26-November 2—**National Infectious Disease Update Conference.** Santa Rosa Kaiser Permanente Medical Center on The Sun Princess Cruise, Western Caribbean. Sat-Fri. 7 hrs. $50-$100. Contact: Infectious Disease Update/SRO, Kaiser Permanente Medical Center, 401 Bicentennial Way, Santa Rosa, CA 95403-2192.

INTERNAL MEDICINE

September 27-October 2—**Internal Medicine 1996—Fall Program.** Continuing Medical Education Associates at Loews Coronado Bay Resort, San Diego. Fri-Wed. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

September 30-October 4—**Texas Internal Medicine Conference.** UCSD at Westgate Hotel, San Diego. Mon-Fri. Contact: UCSD.

NEPHROLOGY

August 2-8—**12th Comprehensive Nephrology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Thurs. 50 hrs. $800. Contact: UCLA.

OCCUPATIONAL MEDICINE

May 31-June 1—**15th Annual Occupational and Environmental Medicine symposium.** UC Davis at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $145. Contact: UCD.

August 5-6—**Worker's Compensation Overview/Update.** UC Berkeley at San Francisco Airport Hilton Hotel. Mon-Tues. 12 hrs. $395. Contact: UC Berkeley.

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(619) 422-1186
FAX (619) 476-1536

August 8-9—**Ergonomics Case Studies: Techniques for Success.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. 13.5 hrs. $395. Contact: UC Berkeley.

December 5-6—**Occupational Disorders of the Upper Extremities.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. Contact: UC Berkeley.

OTOLARYNGOLOGY

June 22-28—**1995-1996 Skull Base Surgical Dissection Course.** House Ear Institute at Los Angeles. Sat-Fri. 65 hrs. $2,500 for two physicians. Contact: House Ear Institute, Antonio De la Cruz, MD, 2100 W Third St, Los Angeles 90057.

June 29-July 4—**Second International Skull Base Congress and the Seventh Annual Meeting of the North American Skull Base Society at Los Angeles.** Sat-Thurs. Contact: Congress Secretary, Ruth B. Crair, House Ear Institute, 2100 W Third St, 5th Floor, Los Angeles 90057.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

July 5-7—**Current Concepts in Allergy and Otolaryngology**. Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital, Continuing Medical Education Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

September 14-18—**1996-1997 Temporal Bone Surgical Dissection Courses**. The House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431-7079.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

October 19-23—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431-7079.

November 7-9— **Otolaryngology Update: 1996**. UCSF at Ritz-Carlton Hotel, SF. Thurs-Sat. 18.5 hrs. $425. Contact: UCSF.

November 9-13—**1996-1997 Temporal Bone Surgical Dissection Courses.** The House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431-7079

December 7-11—**1996-1997 Temporal Bone Surgical Dissection Courses**. The House Ear Institute at Los Angeles. Sat-Wed. 48 hrs. $1,300. Contact: House Ear Institute, (213) 483-4431-7079.

PEDIATRICS

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians**. UCSD at Hilton Beach and Tennis Resort, San Diego. Thurs-Sat. 15 hrs. $350. Contact: UCSD.

July 19-20—**Fourth Annual Pediatric Update**. Stanford University at Lucile Packard Children's Hospital, Palo Alto. Fri-Sat. 14.5 hrs. $275-$300. Contact: Elinor Meyer, CME Coordinator, Lucile Packard Children's Hospital, 725 Welch Road, Palo Alto 94394. (415) 497-8554.

November 9—**Pediatric Pain Management in Managed Care Environment**. Children's Hospital and Health Center at Corning Labs Conference Center, San Diego. Saturday. 7 hrs. $85. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

December 7—**Fifteenth Annual Binational Pediatric Conference.** Children's Hospital and Health Center at Mercy Hospital Education Center, San Diego. Saturday. 5 hrs. $45. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego, 92123. (619) 576-4072.

PLASTIC SURGERY

June 7-9—**The 3rd Annual Course on Lasers in Cutaneous and Cosmetic Surgery.** UCSF at UCSF. Fri-Sun. Contact: UCSF.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation**. UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

June 7-9—**NCGPS Annual Conference.** Northern California Group Psychotherapy Society at Asilomar Conference Center, Pacific Grove. Fri-Sun. Contact: NCGPS, (415) 442-1976.

June 15—**Current Medical Management of Epilepsy.** Scripps Clinic and Research Foundation at La Jolla. Sat. $75. Contact: Dept of Academic Affairs, Box 403C, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

November 2-3—**Neurology Update.** UCSD at Hotel Del Coronado, Coronado. Sat-Sun. 12 hrs. $350. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

November 8-10—**The 42nd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, Coronado. Sat-Thurs. 22.5 hrs. $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

August 15-18—**Minimally Invasive Therapy of the Brain.** UCSD at Ritz-Carlton Hotel, Marina del Rey. Thurs-Sun. 20 hrs. $495. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 24-25—**Neuroradiology Comprehensive Review.** UCSD at Hotel del Coronado, Coronado. Thurs-Fri. 25 hrs. $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 14 hrs. $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 27 hrs. $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

June 26-29—**13th Annual San Diego Shoulder Orthroscopy Meeting.** Tri City Medical Center at Hyatt Regency, La Jolla. Wed-Sat. 24 hrs. $1,375. Contact: Rebecca Quiring, San Diego Shoulder Arthroscopy, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD at San Diego. Mon-Sat. 36 hrs. $1,395. Contact: UCSD.

August 2-3—**Second Annual Surgical Review Postgraduate Course: Review of Lower Gastrointestinal and Breast Diseases.** UC Davis at David Grant Medical Center, Fairfield. Fri- Sat. 14 hrs. $225. Contact: UCD.

August 16-18—**Minimally Invasive Therapy of the Brain.** American Association of Physician Specialists at Ritz-Carlton Hotel, Marina Del Rey. Fri-Mon. 15.5 hrs. $395. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

UROLOGY

November 3-7—**VII World Meeting on Impotence.** American Urological Association and UCSF at Sheraton Palace, San Francisco. Mon-Thurs. $400-$475. Contact: UCSF.

October 5-9—**11th Combined Skin Pathlogy Course & Workshop in Dermatopathology**. UCSD at San Diego Princess. Sat-Wed. 37 hrs. $600. Contact: UCSD.

GENERAL/MULTIDISCIPLINARY

June 12 and 14—**ACLS Instructor Course**. American Heart Association at San Leandro. Wed and Fri. 10 hrs. $219.36. Contact: CPR Seminars, (510) 632-6135.

June 25—**12 Lead EKG.** American Heart Association at San Leandro. Tues. 6 hrs. $95. Contact: CPR Seminars, (510) 632-6135.

July 10—**Pre-ACLS Workshop**. American Heart Association at San Leandro. Wed. 6 hrs. $50-$70. Contact: CPR Seminars, (510) 632-6135.

July 19—**ACLS Recertification**. American Heart Association at San Francisco. Fri. 6 hrs. $100.

July 10 and 21—**ACLS Provider Course.** American Heart Association at San Francisco. 16 hrs. $170. Contact: CPR Seminars, (510) 632-6135.

August 8-11—**38th Annual Postgraduate Refresher Course—Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs. $100. Contact: USC.

August 11-17—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, Hawaii. Mon-Fri. 28 hrs. $590. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. Mon-Wed. 80 hrs. $640. Contact: USC.

August 17-18—**PALS Certification.** American Heart Association at San Leandro. Sat-Sun. 14 hrs. $250. Contact: CPR Seminars, (510) 632-6135.

September 12 & 19—**Arrhythmia Recognition.** American Heart Association at San Leandro. Thurs. 10 hrs. $120. Contact: CPR Seminars, (510) 632-6135.

October 18—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs. $100. Contact: CPR Seminars, (510) 632-6135.

October 19-20—**ACLS Provider.** American Heart Association at San Francisco. Sat-Sun. 16 hrs. $170. Contact: CPR Seminars, (510) 632-6135.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 6-8—**National Stroke Meeting: The Clinical Aspects of Stroke Diagnosis and Treatment.** Medical Education Resources at Red Lion Hotel and Conference Center, Colorado Springs. Thurs-Sat. Contact: Jaclynna Williams, (303) 798-9683. FAX (303) 798-5731.

June 16-22—**42nd Annual Family Practice Review.** University of Colorado Health Sciences Center at Estes Park. Sun-Sat. Contact: U of Colo.

July 14-19—**32nd Annual Internal Medicine Program.** University of Colorado at YMCA of the Rockies, Estes Park. Sun-Fri. Contact: U of Colo.

July 22-26—**Renal Disease and Electrolyte Disorders.** University of Colorado at Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 26-27—**Adenocarcinoma of the Prostate.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

August 4-9—**21st Annual Primary Musculoskeletal Care Conference.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 8-11—**Sixth Annual CME Conference: Women Physicians Finding a Balance, "Keeping the Spark Alive."** Rose Medical Center at Marriott Mountain Resort, Vail. Thurs-Sun. Contact: Ann Wilcox, Rose Medical Center Physician Support Services, (800) 525-1253 or (303) 770-2220.

August 11-13—**First Annual Aspen Brain Tumor Symposium.** University of Colorado at Given Institute, Aspen. Contact: U of Colo.

September 18-21—**Enhancing Quality and Value in Cardiovascular Care.** University of Colorado Health Sciences Center at Vail. Thurs-Sat. Contact: U of Colo.

October 28-November 1—**42nd Annual Family Practice Review (Repeat of June program).** University of Colorado Health Sciences Center at Denver. Mon-Fri. Contact: U of Colo.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo - Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 8-11—**39th Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Mon-Thurs. Contact: Ann Woodrow, CAE, NMAFP, 2309 Renard SE, Albuquerque 87106. (505) 243-4560.

July 11-14—**New Choices, New Challenges, Psychopharmacology in the Primary Care Setting.** La Fonda Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**Podiatric Surgical Seminar.** Hotel Santa Fe, Santa Fe. Wed-Thurs. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 26-28—**How to Diagnose and Treat Arrhythmias for the Primary Care Physician.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

August 2-4—**Practical Pediatrics.** La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 15-18—**Primary Care for the Aging Person.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 22-25—**Implementing Change in Patient Behavior and Clinical Practice.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

September 7-8—**New Mexico Chapter-American College of Surgeons Annual Meeting.** Inn of the Mountain Gods, Ruidoso. Sat-Sun. Contact: Catherine Musemeche, MD, UNM-Division of Pediatric Surgery, 2211 Loma Blvd NE, Albuquerque 87131.

October 3-6—**Building "Virtual" Integrated Delivery Systems: Thriving in an Advanced Healthcare Market.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

June 23-24—**Otolaryngology in the Intermountain West.** University Park Hotel, Salt Lake City. Sun-Mon. 5 hrs. $50. Contact: UUSM.

July 13-20—**Update in Clinical Microbiology and Immunology.** Snow King Resort at Jackson Hole, Wyoming. Sat-Sat. 25 hrs. Contact: UUSM.

August 9-10—**Advanced Obstetrical Life Support.** University Park Hotel, Salt Lake City. 24 hrs. $450. Contact: UUSM.

August 12-16—**Northwest Neuroradiology and Advanced MR Imaging Course.** Pan Pacific Hotel, Vancouver, British Columbia. Mon-Fri. 42 hrs. $1,250. Contact: UUSM.

September 20—**Ophthalmology: Clinical Faculty Day.** Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

October 7-9—**Preconference Workshop.** Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging.** University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology.** Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital, 300 N Hospital Dr, Price 84501. (801) 637-4800.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UANS: Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

VAMC: Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 3-7—**Sampling & Evaluating Airborne Asbestos Dust.** Seattle. Mon-Fri. Contact: NW Center for Occupational Health & Safety. (206) 543-1069.

June 7—**Nuts, Bolts, and Innovation in Gastrointestinal Disease III.** Pierce County College of Medical Education, Tacoma. Fri. Contact: PCMS CME.

June 9-12—**Genome Information: Ethical Implications.** Seattle. Sun-Wed. Contact: U/W Medical History, (206) 616-1864.

June 12-14—**4th Annual Pacific Northwest Cardiovascular Symposium.** Seattle. Wed-Fri. Contact: Providence/Seattle Medical Center, (206) 320-2552.

June 20-21—**ACLS.** Pierce County College of Medical Education, Tacoma. Thurs-Fri. Contact: PCMS CME.

June 28—**Alzheimer's Disease.** Seattle. Fri. Contact: U/W.

June 28—**Cross Cultural Medicine: Healing and Communication in Diverse Cultures.** Tacoma. Fri. Contact: Multicare CME. (206) 552-1221.

July 12-13—**Orthopedic Traumatology.** Seattle. Fri-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 6-8—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

Articles

Clinical Sequelae of Hepatitis C Acquired From Injection Drug Use

MYRON J. TONG, PhD, MD, *and* NEVEEN S. EL-FARRA, *Pasadena, California*

We determined the course of hepatitis C infection in 125 patients with a history of injection drug use. The mean age at presentation was 43.5 years, and the mean age of initiating injection drug use was 23.1 years. Fatigue and hepatomegaly were present in as many as 60% of patients. All had antibodies to the hepatitis C recombinant protein C25, and 99% were positive for hepatitis C virus RNA. After the initial workup, 33 (26%) patients had chronic hepatitis, 46 (37%) had chronic active hepatitis, 45 (36%) had cirrhosis, and 1 (0.8%) presented with hepatocellular carcinoma. During follow-up, hepatocellular carcinoma developed in 2 other patients. In 74 patients with a 1-year history of injection drug use, the mean number of years to the development of chronic hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma were 15.6, 17.6, 19.4, and 26.3 years, respectively. In this subgroup of patients, heavy alcohol abuse did not appear to influence the progression of liver disease. The 2-year case-fatality rate was 2%. Our findings indicate that hepatitis C is a progressive disease, but only a few died during the average 20.4 years after the initiation of injection drug use. Antiviral treatment to eradicate the virus and halt the progression of disease is indicated in this group of patients.

(Tong MJ, El-Farra NS: Clinical sequelae of hepatitis C acquired from injection drug use. West J Med 1996; 164:399-404)

Persons who indulge in injection drug use are prone to infection by blood-borne agents such as the human immunodeficiency virus (HIV), the hepatitis B virus (HBV), and the hepatitis C virus (HCV). In cases of HCV, seroprevalence rates of antibody to HCV in injection drug users seeking medical treatment in an emergency department in Baltimore, Maryland, were 83%, and in those involved in drug treatment programs in Sacramento, California, they were 72%.[1,2] These rates of positivity for antibody to HCV (anti-HCV) in two geographic areas of the United States are similar to those reported in injection drug users in Spain (70%), United Kingdom (81%), Australia (86%), and Amsterdam (74%).[3-6] Comparative studies on the three blood-borne viruses showed that anti-HCV was detected more frequently than hepatitis B surface antigen (6% to 8%) or antibody to HIV (1% to 27%) in injection drug users.[1,2] Therefore, chronic HCV infection is an important health problem in this group of patients.

A report from the Centers for Disease Control and Prevention showed that injection drug use accounted for 36% of the cases of acute hepatitis C in the United States.[7] After acute HCV infection, persistently elevated serum alanine aminotransferase (ALT) levels were detected in as many as 67% of patients. In some patients in whom serum ALT levels returned to normal after acute infection, HCV RNA was still detectable, indicating continual viral replication even in the absence of biochemical evidence of liver inflammation.

There have been few follow-up studies in patients with chronic hepatitis C infection. Two studies showed that the histopathology was less severe and the clinical progression may be slower in patients who acquired their chronic hepatitis C from injection drug use than through blood transfusion.[8,9] Two other reports on patients with posttransfusion hepatitis C indicate that the progression of chronic liver disease was slow and that few had complications after 16 to 18 years of follow-up.[10,11] In contrast, our recent report on a cohort of patients referred to a tertiary care center showed that posttransfusion chronic hepatitis C was a progressive disease and may result in death from either liver failure or hepatocellular carcinoma.[12] To further elucidate the natural history of chronic hepatitis C, we report herein the clinical, biochemical, and histologic findings of patients who acquired their HCV infection through injection drug use.

Patients and Methods

Between December 1981 and October 1994, 170 patients with chronic hepatitis who gave a history of injection drug abuse were evaluated at the Liver Center, Huntington Memorial Hospital, Pasadena, California. All tested positive for antibodies to HCV by methods

From the Liver Center, Huntington Memorial Hospital, Pasadena, California.

The hepatitis C antibody assays for this study were performed by George Kuo, PhD, and David Chien, PhD, from Chiron Corporation, Emeryville, California.

Reprint requests to Myron J. Tong, PhD, MD, Liver Center, Huntington Memorial Hospital, 744 Fairmount Ave, Pasadena, CA 91105.

ABBREVIATIONS USED IN TEXT

AFP = α-fetoprotein
ALT = alanine aminotransferase
anti-HBc = hepatitis B core antibody
anti-HBs = hepatitis B surface antibody
anti-HCV = antibody to HCV
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HCV = hepatitis C virus
HIV = human immunodeficiency virus

described later. Of these patients, 45 were excluded from study because of a coexisting history of blood transfusion and either coinfection with HBV or with HIV. Also, patients with other chronic liver diseases such as hemochromatosis and autoimmune chronic hepatitis were excluded. Thus, 125 patients with injection drug use–associated chronic hepatitis C were analyzed for the following study. Of these, 115 (92%) were referred by their private physician for the following reasons: 108 had abnormal liver test values or a positive anti-HCV antibody test, 6 had symptoms and signs of chronic liver disease, and 1 was referred for evaluation of a liver mass. The remaining 10 patients (8%) were self-referred either from a drug rehabilitation program or because of an abnormal ALT level or a positive anti-HCV antibody test after donating blood.

Liver biopsies were obtained from 112 of the 125 anti-HCV–positive patients. In the remaining 13 patients, liver biopsies were not done because of abnormal coagulation tests; all 13 patients had signs of cirrhosis. Liver biopsies were interpreted according to established histologic criteria, and four liver disease categories were described.[13] Chronic hepatitis had features of portal lymphoid hyperplasia, preservation of the limiting plate, and focal hepatocytolysis. This lesion was formerly referred to as chronic persistent hepatitis.[14] Chronic active hepatitis was diagnosed by the presence of piecemeal necrosis and parenchymal inflammation with or without bridging necrosis. Cirrhosis was characterized by the addition of nodular formation to the above changes. The diagnosis of hepatocellular carcinoma was made by histologic features or by findings of elevated α-fetoprotein (AFP) levels and radiographic changes consistent with this cancer.[15] During follow-up, all patients were screened for hepatocellular carcinoma by testing for AFP levels every six months and with a yearly ultrasound examination of the liver.

A subgroup of patients who gave a history of injecting drugs for a period of a year or less were questioned about alcohol intake. Each was asked to fill out a questionnaire that estimated the time period, type, and the amount of alcohol consumed. The lifetime consumption of alcohol in kilograms was estimated by using the following criteria: 12 oz beer = 4 oz wine = 1 oz liquor = 13 grams of alcohol.[16]

Laboratory Tests

The sera of patients were tested for HCV RNA by polymerase chain reaction as previously described.[14] All patients were tested for HCV antibodies by Chiron Corporation assays.[17] The antigens used were the chimeric C25 protein, which included C22, C100-3, and C33C, and the individual HCV recombinant proteins C22, E1, E2, NS3, C100-3, and NS5. The liver tests were measured by the Hitachi 747, Boeringer Manuheim, Indianapolis, Indiana. The AFP was assayed by Nichols Institute, San Juan Capistrano, California. The upper limit of normal for AFP was 18 μg per liter.

Hepatitis B Antibody Tests

Antibodies to hepatitis B surface antigen (anti-HBs) and to hepatitis B core antigen (anti-HBc) were measured by radioimmunoassay (AusAb and CorAB, Abbott Laboratories, North Chicago, Illinois).

Analysis

Data for each study variable were analyzed for the arithmetic mean and standard deviation of the mean. Statistical analysis was performed by the *t* test; all *P* values are two-tailed.

Results

Clinical Characteristics of Patients

During the first visit to the Liver Center, the average age of the 125 patients with a history of injection drug use was 43.5 years (range, 28 to 70 years). The average age at the time of initiating self-injection of drugs was 23.1 years (range, 8 to 60 years). There were 37 women and 88 men. The ethnic background of the 125 patients included 102 white, 3 Asian, 15 Hispanic, and 5 African American. The mean follow-up after presentation was 21 months (range, 1 to 115 months).

The estimated length of time of injection drug use in the 125 anti-HCV–positive patients varied. A total of 74 patients (59%) admitted to self-injecting drugs for a period of only one year or less, 23 patients (18%) for two to five years, and 13 patients (10%) for six to ten years. In addition, ten patients self-injected drugs for 20 years, four patients for 30 years, and one patient for 40 years. An episode of acute hepatitis characterized by jaundice, fatigue, and dark urine within six months of injection drug use was reported by 35 patients (28%).

Hepatitis C Viral Antibodies and Hepatitis C Viral RNA

Analysis of the antibody profiles to recombinant HCV antigens showed that all 125 patients had antibodies to C25 chimeric protein. Antibodies to C22, NS3, NS5, and C100-3 were detected in 98%, 95%, 76%, and 74% of patients, respectively. Antibodies to structural proteins E1 and E2 were found in 56% and 45% of patients. The HCV RNA was positive in 124 of 125 (99%) of these patients.

Hepatitis B Viral Antibodies

Evidence for past hepatitis B infection was present in 42 of 92 (46%) anti-HCV–positive patients who had HBV antibody tests performed. Anti-HBs only was

TABLE 1.—*Presenting Symptoms and Signs by Liver Disease Category of 125 Patients With Hepatitis C Acquired by Injection Drug Use*

Symptom or Sign	Chronic Hepatitis (n = 33)* No. (%)	Chronic Active Hepatitis (n = 46)* No. (%)	Cirrhosis*† (n = 46) No. (%)	Total No. of Patients (n = 125)* No. (%)
Fatigue	21 (64)	25 (54)	33 (72)	79 (63)
Abdominal pain	5 (15)	16 (35)	13 (28)	34 (27)
Anorexia	2 (6)	4 (9)	11 (24)	17 (14)
Weight loss	2 (6)	4 (9)	6 (13)	12 (10)
Jaundice	0 (0)	0 (0)	4 (9)	4 (3)
Hepatomegaly	13 (39)	23 (50)	36 (78)	72 (58)
Splenomegaly	3 (9)	2 (4)	18 (39)	23 (18)

*Number of patients in each disease category.
†One patient with cirrhosis presented with hepatocellular carcinoma.

detected in 4 (4%), anti-HBc only in 15 (16%), and both antibodies were present in 23 patients (25%).

Clinical and Laboratory Findings on Presentation

The presenting symptoms and signs of 125 anti-HCV–positive patients are shown in Table 1. Fatigue (63%) was the most common complaint, followed by abdominal pain (27%), anorexia (14%), and weight loss (10%). Jaundice was present in only four patients (3%) with cirrhosis. Hepatomegaly and splenomegaly were detected in 58% and 18%, respectively. The mean presenting laboratory test values included albumin, 42 grams per liter (range, 28 to 54); bilirubin, 15.2 μmol per liter (range, 3.42 to 112.9); aspartate aminotransferase, 100 U per liter (range 18 to 322); and ALT, 156 U per liter (range, 19 to 554).

Liver Disease Classification

After the initial workup, the diagnoses for the 125 anti-HCV–positive patients included 33 (26%) with chronic hepatitis, 46 (37%) with chronic active hepatitis, and 46 (37%) with cirrhosis. When presenting symptoms were assessed by liver disease categories, fatigue was the most common complaint in each disorder (Table 1). In the 46 patients with cirrhosis, 22 (48%) had splenomegaly with thrombocytopenia (mean platelet count, 71.6×10^3 per mm^3; range, 35 to 102), 14 (30%) had ascites, 8 (17%) had esophageal varices, and 4 (9%) had hepatic encephalopathy.

One of the anti-HCV–positive patients with cirrhosis presented with hepatocellular carcinoma. In two other patients with cirrhosis, hepatocellular carcinoma also developed at 18 months and 32 months, respectively, during the follow-up period. The mean AFP level of the three patients with hepatocellular carcinoma was 6,094 μg per liter (range, 1.6 to 17,833). The mean AFP level in all patients without hepatocellular carcinoma was 6.9 μg per liter (range, 1.6 to 120.5). The serum AFP values were consistently normal in patients with chronic hepatitis and with chronic active hepatitis and were above the normal range in 3 (7%) cirrhotic patients without hepatocellular carcinoma (30, 43.7, and 120.5 μg per liter, respectively).

The mean intervals between the time of the initiation of injecting drugs to the time of the diagnosis of either chronic hepatitis, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma are shown in Figure 1. Only the 74 patients who gave a history of a year or less of drug abuse were used for this analysis because it was not possible to predict the time of exposure to HCV in the remaining patients whose time period of self-injecting drugs ranged from 2 to 40 years. Thus, in the above-mentioned 74 patients, the mean number of years from injection drug use to chronic hepatitis was 15.6 years (range 8 to 23 years), to chronic active hepatitis was 17.6 years (range 12 to 24 years), to cirrhosis was 19.4 years (range 11 to 28 years), and it was 26 years (range 18 to 34 years) for the three patients with hepatocellular carcinoma.

Effect of Alcohol Intake on Liver Disease Progression

In an attempt to determine the effect of heavy alcohol consumption on the clinical course of hepatitis C, we interviewed the 74 anti-HCV–positive patients who gave a one-year history or less of injection drug use and divided this cohort into those with and without admitted alcohol abuse. Within this group of 74 patients, 53 (72%) gave a history of heavy alcohol consumption while 21 denied alcohol use. Each patient was asked to estimate the time period of alcohol consumption and the approximate amount of alcohol that was consumed. For those who admitted to heavy alcohol abuse, the time period of use was divided into drinking for 5 years, 6 to 10 years, 11 to 20 years, and for 21 to 40 years. The estimated average number of drinks per day was obtained by history, and the average lifetime consumption of alcohol in kilograms was then calculated. In the 53 patients who admitted to heavy alcohol consumption, the estimated average lifetime consumption of alcohol ranged from 277 kg for those with 5 years of abuse, 471 kg for those with as long as 10 years of abuse, 736 kg for those with as long as 20 years of abuse, and 1,984 kg for the patients with as long as 40 years of alcohol use. In the 21 patients who denied heavy alcoholic use, the estimated average lifetime consumption of alcohol was calculated to be 6.5 kg. When the average time for the development

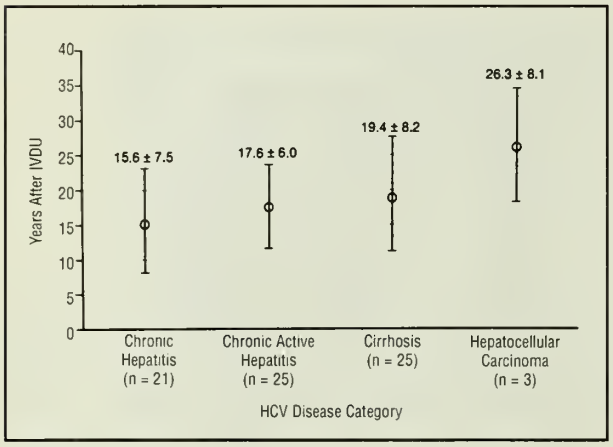

Figure 1.—The graph shows the mean time interval expressed in years plus-minus standard deviation from the time of intravenous drug use (IVDU) to presentation with diseases associated with hepatitis C in 74 patients with a 1-year history of intravenous drug use. HCV = hepatitis C virus

of each liver disease category was compared in these 74 patients with and without heavy alcohol abuse, there were no significant time differences noted (14.9 years versus 17.3 years for chronic hepatitis, 18.2 years versus 16.1 years for chronic active hepatitis, and 21.4 years versus 16.9 years for cirrhosis; $P > .20$ in all categories).

Disease Outcome

The overall two-year case-fatality rate in our anti-HCV–positive patients with a history of injection drug use was 2% (3 of 125 patients). One patient died of hepatocellular carcinoma, and two patients died of complications after liver transplantation. Two other patients, one with cirrhosis and one with hepatocellular carcinoma, who also underwent orthotopic liver transplantation are still living at the time of this writing.

Discussion

Hepatitis C infection is a common disease in injection drug users.[1,2] A recent report showed that 71.4% of persons with a history of less than a year of injection drug use were anti-HCV–positive, whereas 91.7% of those who self-injected drugs for more than ten years had antibodies to HCV.[18] These last findings indicate that HCV is commonly transmitted to newer initiates of injection drug use and that a longer duration of use was significantly associated with increasing anti-HCV–positivity. In our report, virtually all (124 of 125) of the anti-HCV–positive patients were HCV RNA–positive. Therefore, it is not surprising that the sharing of needles among injection drug users would result in high rates of HCV transmission.

Hepatitis B infection is also common in injection drug users. In this report, we excluded patients with coexisting hepatitis B infection because the presence of both HBV and HCV may accelerate the rate of liver disease progression. In fact, all three patients with both HBsAg– and anti-HCV–positivity who were excluded from this study had cirrhosis. Past exposure to hepatitis B was evident in this group of injection drug users because hepatitis B antibodies were detected in 45% of our anti-HCV–positive patients. In another report, anti-HBc was detected in 71% and anti-HBs in 51% of injection drug users enrolled in drug treatment programs.[2] Thus, both hepatitis B and C viruses are important pathogens in the injection drug user population.

More than 90% of our patients had detectable antibodies to the HCV recombinant proteins C22 and NS3, 70% had antibodies to NS5 and C100-3, and about 50% had antibodies to the structural proteins E1 and E2. The frequency of antibodies to the individual HCV proteins in our patients with a history of injection drug abuse was similar to our findings in patients with posttransfusion hepatitis C[12] and hence may represent a general pattern of antibody response to these recombinant antigens that is observed after hepatitis C infection regardless of the mode of transmission. The reasons for only a 50% positivity for antibodies to the reputed envelope proteins E1 and E2 are unclear, but they may be due to the fact that these recombinant antigens are linear instead of conformational in configuration.

Our results indicate that fatigue was a common symptom among anti-HCV–positive patients and was present in more than 50% of those with chronic hepatitis, chronic active hepatitis, and cirrhosis. Hepatomegaly was a common finding and was noted more frequently as the liver disease category progressed in severity. These clinical observations are similar to those reported in patients with transfusion-associated hepatitis C.[12] In the latter study, more than 65% of anti-HCV–positive patients presented with fatigue, and hepatomegaly also was frequently detected. Therefore, in our experience at a tertiary care center, patients with hepatitis C commonly presented with symptoms and signs of chronic liver disease. This is in contrast with other reports that indicated that patients with transfusion-associated chronic hepatitis C had few clinical symptoms and signs of liver disease even when observed for 16 to 18 years after HCV infection.[10,11]

In 74 of our patients who gave a history of injection drug use for a year or less, the mean times for the development of chronic hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma were 15.6 years, 17.6 years, 19.4 years, and 26.3 years, respectively. These time intervals for the progression of liver disease are similar to those reported for patients with posttransfusion chronic hepatitis C in Japan,[19,20] as well as for transfused patients in the United States.[12] Altogether, these observations indicate that the time of the initial HCV infection may be the major determinant of the type of liver disease that is encountered during an initial presentation to a physician. There are patients, however, who are infected with HCV who do not fit into the above characterizations. Other factors, such as HCV genotypes and viral titers, also may influence the progression of chronic liver disease in these persons.[21-23] One report noted that closely related hepatitis C viral sequences

were detected by polymerase chain reaction in injection drug users, suggesting that they were infected from a common source.[24] Subsequently, specific HCV genotyping of injection drug users showed that types 1a and 3a were more frequently detected in this group of patients in Italy,[25] and genotype 3a was more prevalent in injection drug users in Scotland.[26] A report from Japan suggested that HCV genotypes may not be responsible for the development of serious liver disease because no significant differences in the distribution of any of the genotypes were detected among patients in different stages of chronic liver disease.[27] In one study on the quantitation of serum HCV RNA, injection drug users had a lower median viremia level than patients infected by blood transfusion, and no differences in HCV-RNA values were noted in patients with either chronic hepatitis, chronic active hepatitis, or cirrhosis.[27,28] Other investigators noted, however, that HCV-RNA levels were similar in transfused patients and in injection drug users.[29] The latter report also showed that patients with histologic findings of chronic hepatitis had lower viremia levels than those with chronic active hepatitis or cirrhosis. Further studies are needed to elucidate the role of viral genotypes and of HCV-RNA levels in determining the clinical outcome of injection drug users with chronic hepatitis C infection.

In this report, we attempted to determine the contribution of heavy alcohol abuse to the progression of liver disease in HCV-infected injection drug users. The estimates for the time of alcohol intake and the amount of alcohol consumed relied on memory and on the patients' willingness to even admit to alcohol abuse. For this purpose, we only included patients with a history of one year or less of injection drug use because this is the only group in whom we could predict the alleged time of initial HCV infection. Therefore, 74 patients were interviewed regarding alcohol intake. Of these, 71% admitted to heavy alcohol abuse, and 29% indicated either no alcohol intake or only occasional use. For the patients with heavy alcohol abuse, the estimated total lifetime amount consumed ranged from an average of 277 kg in those who imbibed for 5 years to an average of 1,984 kg for those who imbibed for as long as 40 years. These values were compared with a lifetime consumption of an average of only 6.5 kg in the patients who said they drank little or no alcohol. Using the above measures, we found no differences in the time of progression to chronic hepatitis, chronic active hepatitis, or cirrhosis when patients with a history of prolonged alcohol intake were compared with those without a drinking history. Based on these findings, the excessive use of alcohol in this subgroup of patients did not appear to hasten the progression of liver disease when compared with those with little or no alcohol consumption. Other reports showed a high prevalence of anti-HCV–positivity in patients with alcoholic liver disease, and it was suggested that HCV infection may have accelerated the progression to cirrhosis in these persons.[16,30-32] In our patients, however, chronic hepatitis C infection from injection drug use probably was the primary cause of their liver disease, and their alcohol intake may not have been as heavy or as prolonged as those patients in previous reports who were considered to have established alcoholic liver disease and then incidentally found to be anti-HCV–positive. Further studies are needed to clarify the association between chronic hepatitis C infection and alcohol intake.

In this report of hepatitis C infection associated with injection drug use, the mortality rate was 2%, and hepatocellular carcinoma developed in three patients. The average age of our patients at presentation to a tertiary care center, however, was relatively young (43.5 years), and the average time period from initial HCV infection was about 20.4 years. The relatively low morbidity and mortality in our patients is similar to those reported for patients with posttransfusion hepatitis C who had been observed for periods of 16 and 18 years.[10,11] Therefore, it is conceivable that more of our patients will progress to serious liver disease or hepatocellular carcinoma as they advance in age and as the time of the HCV infection becomes more prolonged. Such was the observation in our patients with transfusion-associated chronic hepatitis C.[12] Whether these outcomes will be the case or whether the course of hepatitis C infection is less severe and has a slower progression in patients who acquire their HCV from injection drug use rather than by transfusion[8,9] will only be clarified with long-term follow-up of these persons.

In summary, our findings indicate that hepatitis C associated with injection drug use is a progressive disease, and serious liver complications may develop with time. Both proper education concerning the transmission of HCV in these patients and practical measures to prevent infection must be continued by public health officials. Finally, antiviral therapy should be attempted to eliminate the virus and to prevent progression of this chronic viral illness.

REFERENCES

1. Kelen GD, Green GB, Purcell RH, et al: Hepatitis B and hepatitis C in emergency department patients. N Engl J Med 1992; 326:1399-1404

2. Zeldis JB, Jain S, Kuramoto IK, et al: Seroepidemiology of viral infections among intravenous drug users in northern California. West J Med 1992; 156: 30-35

3. Esteban JI, Esteban R, Viladomiu L, et al: Hepatitis C virus antibodies among risk groups in Spain. Lancet 1989; 2:294-297

4. Mortimer PP, Cohen BJ, Litton PA, et al: Hepatitis C virus antibody (Letter). Lancet 1989; 2:798

5. Bell J, Batey RG, Farrell GC, Crewe EB, Cunningham AL, Byth K: Hepatitis C virus in intravenous drug users. Med J Aust 1990; 153:274-276

6. van den Hoek JAR, van Haastrecht HJA, Goudsmit J, de Wolf F, Coutinho RA: Prevalence, incidence, and risk factors of hepatitis C virus infection among drug users in Amsterdam. J Infect Dis 1990; 162:823-826

7. Alter MJ: The detection, transmission, and outcome of hepatitis C virus infection. Infect Agents Dis 1993; 2:155-166

8. Mattsson L, Weiland O, Glaumann H: Chronic non-A, non-B hepatitis developed after transfusions, illicit self-injections or sporadically—Outcome during long-term follow-up: a comparison. Liver 1989; 9:120-127

9. Gordon SC, Elloway RS, Long JC, Dmuchowski CF: The pathology of hepatitis C as a function of mode of transmission: Blood transfusion vs. intravenous drug use. Hepatology 1993; 18:1338-1343

10. Koretz RL, Abbey H, Coleman E, Gitnick G: Non-A non-B post-transfusion hepatitis—Looking back in the second decade. Ann Intern Med 1993; 119:110-115

11. Seeff LB, Buskell-Bales Z, Wright EC, et al: Long-term mortality after transfusion-associated non-A non-B hepatitis—The National Heart, Lung, and Blood Institute Study Group. N Engl J Med 1992; 327:1906-1911

12. Tong MJ, El-Farra NS, Reikes AR, Co RL: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332:1463-1466

13. Boyer JL: Chronic hepatitis—A perspective on classification and determinants of prognosis. Gastroenterology 1976; 70:1161-1171

14. Ludwig J: The nomenclature of chronic active hepatitis: An obituary. Gastroenterology 1993; 105:274-278

15. Tong MJ, Lee SY, Hwang SJ, et al: Evidence for hepatitis C viral infection in patients with primary hepatocellular carcinoma. West J Med 1994; 160:133-138

16. Caldwell SH, Li X, Rourk RM, et al: Hepatitis C infection by polymerase chain reaction in alcoholics: False-positive ELISA results and the influence of infection on a clinical prognostic score. Am J Gastroenterol 1993; 88:1016-1021

17. Chien DY, Choo QL, Tabrizi A, et al: Use of recombinant HCV antigen in the serodiagnosis of hepatitis C virus infection: Significant improvement in HCV antibody detection as compared with the first generation HCV C100-3 ELISA and the synthetic peptide ElA tests. J Gastroenterol Hepatol 1993; 8:S33-S39

18. Donahue JG, Nelson KE, Muñoz A, et al: Antibody to hepatitis C virus among cardiac surgery patients, homosexual men, and intravenous drug users in Baltimore, Maryland. Am J Epidemiol 1991; 134:1206-1211

19. Kiyosawa K, Sodeyama T, Tanaka E, et al: Interrelationship of blood transfusion, non-A non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. Hepatology 1990; 12(pt 1):671-675

20. Takahashi M, Yamada G, Miyamoto R, Doi T, Endo H, Tsuji T: Natural course of chronic hepatitis C. Am J Gastroenterol 1993; 88:240-243

21. Dusheiko G, Schmilovitz-Weiss H, Brown D, et al: Hepatitis C virus genotypes: An investigation of type-specific differences in geographic origin and disease. Hepatology 1994; 19:13-18

22. Mita E, Hayashi N, Kanazawa Y, et al: Hepatitis C virus genotype and RNA titer in the progression of type C chronic liver disease. J Hepatol 1994; 21:468-473

23. Nousbaum JB, Pol S, Nalpas B, et al: Hepatitis C virus type 1b (II) infection in France and Italy. Ann Intern Med 1995; 122:161-168

24. Simmonds P, Zhang LQ, Watson HG, et al: Hepatitis C quantification and sequencing in blood products, haemophiliacs, and drug users. Lancet 1990; 336:1469-1472

25. Silini E, Bono F, Cividini A, et al: Molecular epidemiology of hepatitis C virus infection among intravenous drug users. J Hepatol 1995; 22:691-695

26. Chan SW, McOmish F, Holmes EC, et al: Analysis of a new hepatitis C virus type and its phylogenetic relationship to existing variants. J Gen Virol 1992; 73(pt 5):1131-1141

27. Yamada M, Kakumu S, Yoshioka K, et al: Hepatitis C virus genotypes are not responsible for development of serious liver disease. Dig Dis Sci 1994; 39: 234-239

28. Lau JYN, Davis GL, Kniffen J, et al: Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993; 341:1501-1504 [erratum published in Lancet 1993; 342:504]

29. Gordon SC, Kodali VP, Silverman AL, et al: Levels of hepatitis C virus RNA and liver histology in chronic type C hepatitis. Am J Gastroenterol 1994; 89:1458-1461

30. Poynard T, Aubert A, Lazizi Y, et al: Is hepatitis C virus infection a cause of cirrhosis among drinkers? *In* Hollinger FB, Lemon SM, Margolis HS (Eds): Viral Hepatitis and Liver Disease—International Symposium on Viral Hepatitis and Liver Disease: Contemporary Issues and Future Prospects. Baltimore, Md, Williams & Wilkins, 1990, pp 681-683

31. Laurent-Puig P, Dussaix E, Lecoz Y, Martes P, Buffet C: Prevalence of anti-hepatitis C virus antibodies among patients with alcoholic liver disease, supplemented by 4-RIBA (Letter). Dig Dis Sci 1992; 37:156-157

32. Zarski JP, Thelu MA, Moulin C, Rachail M, Seigneurin JM: Interest of the detection of hepatitis C virus RNA in patients with alcoholic liver disease. J Hepatol 1993; 17:10-14

Articles

Differing Beliefs About Breast Cancer Among Latinas and Anglo Women

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To improve breast cancer control among Latinas, it is important to understand culturally based beliefs that may influence the way women view this disease. We did a telephone survey of randomly selected Latinas and non-Hispanic white (Anglo) women in Orange County, California, to explore such beliefs using questions from previous national surveys and an ethnographic study of breast cancer. Respondents included 803 Latinas and 422 Anglo women. Latinas were more likely than Anglo women to believe that factors such as breast trauma (71% versus 39%) and breast fondling (27% versus 6%) increased the risk of breast cancer, less likely to know that symptoms such as breast lumps (89% versus 98%) and bloody breast discharge (69% versus 88%) could indicate breast cancer, and more likely to believe that mammograms were necessary only to evaluate breast lumps (35% versus 11%) ($P <$ .01 for each). After adjusting for age, education, employment status, insurance status, and income, logistic regression analysis confirmed that Latino ethnicity and acculturation levels were significant predictors of these beliefs. We conclude that Latinas' beliefs about breast cancer differ in important ways from those of Anglo women and that these beliefs may reflect the moral framework within which Latinas interpret diseases. These findings are important for the development of culturally sensitive breast cancer control programs and for practicing physicians.

(Hubbell FA, Chavez LR, Mishra SI, Valdez RB: Differing beliefs about breast cancer among Latinas and Anglo women. West J Med 1996; 164:405-409)

Despite advances in screening and treatment during the past several decades, breast cancer remains a major health problem for women of all ethnic groups in the United States. An estimated 12% of all women will receive a diagnosis of breast cancer, and 3.5% will die of the disease.[1] Although Latinas (Hispanic women) have somewhat lower incidence rates of breast cancer than Anglo (non-Hispanic white) women, they are more likely to have larger tumors or metastatic disease (or both) at the time of diagnosis.[2,3] Moreover, they are less likely to receive appropriate breast cancer screening.[4,5] Although the socioeconomic reasons for the lower screening rates, such as high rates of poverty and lack of health insurance, have been well defined,[6-8] much less information exists about culturally based beliefs that may influence the way Latinas view breast cancer. The purpose of this study was to explore such beliefs among Latinas and Anglo women in Orange County, California, through a large telephone survey.

Subjects and Methods

Orange County is a community of about 2.5 million residents located in southern California.[9] About 23% of the county's population is Latino, and 45% is Anglo. Most Latinos are of Mexican heritage; however, an estimated 25,000 immigrants from Central America, particularly from El Salvador, also live in the county.

To obtain information about breast cancer-related knowledge and attitudes, trained bilingual women interviewers from the Field Research Corporation in San Francisco, California, conducted a telephone survey of randomly selected Latinas and Anglo women during September 1992 to March 1993. We designed the survey instrument using questions from the National Health Interview Survey and its Cancer Control Supplement,[10] the Behavioral Risk Factor Surveillance Survey,[11] and a previously validated acculturation scale.[12] In addition, we included questions from a previous ethnographic survey that revealed that Latinas, particularly immigrants, frequently believed that factors such as trauma to the breast and having many sexual partners increased the risk of breast cancer.[13] They also expressed misconceptions about breast cancer screening, such as that mammograms were necessary only if there was a breast lump. Therefore, we included questions to explore the frequency of such beliefs among respondents in the telephone survey. Bilingual investigators translated the questions

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from English to Spanish and then back-translated them using well-established procedures.[14] They revised the questionnaire after pretesting it in a random sample of Latinas and Anglo women not involved with the study. The response categories for the questions regarding knowledge about risk factors and symptoms were "yes," "no," "don't know," and "refused to answer." Response categories for the attitudinal questions were "agree," "disagree," "don't know," and "refused to answer." The final questionnaire took an average of 35 minutes to complete.

The survey used the computer-assisted telephone interview system and a cross-sectional sample of random-digit telephone listings that included all numbers, avoiding possible bias due to exclusion of households with unlisted numbers.[15] Eligible participants were English- or Spanish-speaking women 18 years of age or older who were not institutionalized and who identified themselves as Latina (Hispanic or more specific ethnic identifiers such as Mexican or Mexican American) or Anglo (non-Hispanic white). We designed the sampling strategy to oversample Latino households, with the goal of obtaining about twice as many Latino respondents as Anglo respondents. The survey randomly selected both households and respondents within households—the woman 18 years or older who had the most recent birthday. Latina respondents could choose to answer the questions in Spanish or English. The University of California, Irvine, Human Subjects Review Committee approved the research protocol. All participants provided oral informed consent.

We categorized risk factors and symptoms as reasonable or less reasonable and attitudes as favorable and less favorable based on the medical literature.[1] The analysis combined "no" and "don't know" categories for the knowledge questions and treated the "don't know" category as missing data for the attitudinal questions. We used the two-tailed χ^2 test to analyze the categorical data and logistic regression analysis to evaluate the relative contribution of ethnicity in predicting knowledge and attitudes about breast cancer. Predictor variables included ethnicity (Anglo = 0, Latina = 1), age (≤40 = 0, >40 = 1), marital status (married = 0, not married = 1), household income (≤$25,000 = 0, >$25,000 = 1), insurance status (insured = 0, not insured = 1), education (≤high school = 0, >high school = 1), employment status (employed = 0, not employed and not in the work force = 1), and acculturation level for the Latina sample only (high = 0, low = 1). The results appear as odds ratios, calculated by computing the exponential of the β value and 95% confidence intervals.[16] The confidence intervals provided a basis for evaluating the magnitude of the differences between Latinas and Anglo women even if these differences were not statistically significant.[17]

Results

Respondents

Interviewers made 21,171 calls, of which 1,561 (7.4%) were to eligible women. They completed interviews with 1,225 of the 1,561 eligible women for an overall cooperation rate of 78.5%—defined as the number of completed interviews divided by the sum of the completed interviews and refusals by eligible women (1,225/[1,225 + 336]). The response rate for Latinas (75%) was lower than that for Anglo women (87%). Of the remaining calls, 9,850 (46.5%) were to business or disconnected numbers, 8,002 (37.8%) were to ineligible households, 1,315 (6.2%) were to women who refused to participate before eligibility screening, and 443 (2.1%) were to households that did not answer.

TABLE 1.—*Demographic Characteristics of Latinas and Anglo Women**

Characteristic	*Latinas, % (n = 803)*	*Anglo Women, % (n = 422)*
Age, years		
<40	74	47
40-49	15	23
>49	11	31
Education, years		
0-6	22	<1
7-12	43	25
>12	35	75
Annual household income, $		
<10,000	18	7
10,000-29,999	44	23
>29,999	39	70
Health insurance		
Insured	67	92
Not insured	33	8
Employment status		
Full-time	43	50
Part-time	12	12
Not employed	45	38
Country of birth		
United States	34	100
Mexico	53	0
Other	13	0
Acculturation		
More	38	NA
Less	62	NA

NA = not applicable

*The sum of the proportions does not always equal 100% because of rounding error.

Of the 1,225 women interviewed, 803 were Latinas and 422 were Anglo women. Their demographic characteristics appear in Table 1. Compared with the Anglo women, the Latinas were younger (mean age, 33.9 versus 43.8 years), had less education (mean, 10.9 versus 14.5 years), had lower household income levels (median yearly income, $17,000 versus $48,000), and were less likely to have health insurance (67% versus 92%). Most of the Latinas were born outside the United States (66%) and had low acculturation levels (62%).

Bivariate Analysis

Table 2 displays bivariate analysis of knowledge and attitudes about breast cancer among Latinas and Anglo women. Latinas were less likely than Anglo women to embrace medically accepted risk factors such as family history and more likely to believe that other factors such

TABLE 2.—*Knowledge and Attitudes About Breast Cancer Among Latinas and Anglo Women*

Knowledge and Attitude	*Latinas (n = 803), % Yes/Agree**	*Anglo Women (n = 422), % Yes/Agree**
Knowledge about risk factors		
Reasonable		
Family history	84†	98
Age	58†	73
Birth control pills	65	65
Radiation	52	57
First child after age 30	30	27
Early menses	12	16
Less reasonable		
Breast trauma	71†	39
Breast implants	84†	66
Chemicals in food	65	67
Worrying	37†	28
Fate	35†	22
Multiple sexual partners	36†	9
Antibiotics	26†	7
Breast fondling	27†	6
Knowledge about symptoms		
Reasonable		
Breast lump	89†	98
Bloody breast discharge	69†	88
Puckered breast skin	44†	63
Less reasonable		
Painful breast	70	69
Differing breast size	51	47
Attitudes		
Favorable		
If breast cancer is found early, it can be cured	98	98
I would undergo breast cancer treatment that is unpleasant or painful if it would improve my chances of living longer	94	93
Less favorable		
I am likely to get breast cancer in my lifetime	57†	32
There is not much I can do to prevent breast cancer	30†	22
I only need a mammogram when I have a breast lump	35†	11
I would be afraid to tell my husband or partner if I had breast cancer because it would affect our relationship	15†	3
I would rather not know if I had breast cancer	17†	3

*We asked participants to respond "yes" or "no" to the knowledge questions and to "agree" or "disagree" with the attitudinal questions.

†$P < .01$ between Latinas and Anglo women.

as breast trauma increased the risk of contracting breast cancer. A smaller proportion of Latinas than Anglo women believed that a breast lump, bloody breast discharge, and puckering of the skin over the breast were symptoms of breast cancer. In addition, Latinas more often had less favorable attitudes such as the belief that they needed a mammogram only when they had a breast lump, feared telling their husbands if they had breast cancer, and were reluctant to know if they had the disease.

Multivariate Analysis

Findings from the multivariate analysis supported those from the bivariate analysis (Table 3). After controlling for age, marital status, household income, insurance status, education, and employment status, the Latinas were still more likely to have misconceptions about risk factors and symptoms of breast cancer and to have less favorable attitudes about the disease. Years of formal education and income levels also significantly predicted knowledge about some risk factors and symptoms and some unfavorable attitudes (data not shown). For example, women with a high school or more education were more likely to know that breast lumps could be a symptom of breast cancer (odds ratio [OR] = 2.4, $P < .001$) and were less likely to believe that a woman needed a mammogram only when she had a breast lump (OR = 0.5, $P = .002$). Likewise, women with income levels

TABLE 3.—*Adjusted Odds Ratios of Latino Ethnicity as a Predictor of Knowledge and Attitudes about Breast Cancer**

Knowledge and Attitude	*Odds Ratio*	*95% CI*	P
Knowledge about risk factors			
Reasonable			
Family history	0.3	0.1–0.7	.01
Age	0.7	0.5–1.0	.03
Birth control pills	1.0	0.7–1.4	NS
Radiation	1.0	0.7–1.3	NS
First child after age 30	1.0	0.8–1.4	NS
Early menses	0.7	0.4–1.1	NS
Less reasonable			
Breast trauma	3.0	2.1–4.1	<.001
Breast implants	2.0	1.4–2.9	<.001
Chemicals in food	0.7	0.5–1.0	NS
Worrying	0.8	0.6–1.2	NS
Fate	0.9	0.6–1.3	NS
Multiple sexual partners	4.3	2.4–7.7	<.001
Antibiotics	1.6	1.0–2.8	NS
Breast fondling	3.2	1.8–5.8	<.001
Knowledge about symptoms			
Reasonable			
Breast lump	0.4	0.2–0.9	.05
Bloody breast discharge	0.6	0.4–0.9	.05
Puckered breast skin	0.6	0.4–0.9	.01
Less reasonable			
Painful breast	1.0	0.7–1.5	NS
Differing breast size	1.2	0.9–1.7	NS
Attitudes			
Favorable			
Can be cured	1.7	0.6–5.0	NS
Would undergo treatment	1.8	0.9–3.6	NS
Less favorable			
Likely to get	1.6	1.1–2.3	.01
Can't prevent	1.0	0.7–1.6	NS
Rather not know	2.7	1.1–6.8	.03
Afraid to tell husband	3.0	1.3–7.0	.01
Mammogram only for lump	1.8	1.2–2.9	.01

CI = confidence interval, NS = not significant

*Adjusted for age (≤40 = 0, >40 = 1), marital status (married = 0, not married = 1), household income (≤$25,000 = 0, >$25,000 = 1), insurance status (insured = 0, not insured = 1), education (≤high school = 0, >high school = 1), and employment status (employed = 0, not employed and not in the work force = 1).

TABLE 4.—*Adjusted Odds Ratios of Acculturation Level as a Predictor of Knowledge and Attitudes About Breast Cancer, Latinas Only**

Knowledge and Attitude	*Odds Ratio*	*95% CI*	P
Knowledge about risk factors			
Reasonable			
Family history	0.1	0.1–0.4	<.001
Age	0.5	0.3–0.8	<.001
Birth control pills	0.9	0.6–1.3	NS
Radiation	1.1	0.7–1.7	NS
First child after age 30	1.8	1.1–2.9	.01
Early menses	1.0	0.5–1.9	NS
Less reasonable			
Breast trauma	4.2	2.6–6.8	<.001
Breast implants	3.0	1.7–5.3	<.001
Chemicals in food	1.7	1.1–2.6	.01
Worrying	2.2	1.4–3.6	<.001
Fate	1.6	1.0–2.6	.04
Multiple sexual partners	6.7	3.9–11.4	<.001
Antibiotics	3.2	1.8–5.7	NS
Breast fondling	3.9	2.2–6.7	<.001
Knowledge about symptoms			
Reasonable			
Breast lump	0.4	0.2–0.9	.02
Bloody breast discharge	0.4	0.2–0.6	<.001
Puckered breast skin	0.8	0.5–1.1	NS
Less reasonable			
Painful breast	0.7	0.4–1.1	NS
Differing breast size	1.5	1.0–2.3	.04
Attitudes			
Favorable			
Can be cured	1.4	0.3–6.5	NS
Would undergo treatment	1.0	0.4–2.5	NS
Less favorable			
Likely to get	2.1	1.4–3.2	<.001
Can't prevent	1.0	0.6–1.7	NS
Rather not know	5.1	2.1–12.2	<.001
Afraid to tell husband	1.7	0.8–6.7	NS
Mammogram only for lump	1.4	0.9–2.3	NS

CI = confidence interval, NS = not significant

*Adjusted for age (≤40 = 0, >40 = 1), marital status (married = 0, not married = 1), household income (≤$25,000 = 0, >$25,000 = 1), insurance status (insured = 0, not insured = 1), education (≤high school = 0, >high school = 1), and employment status (employed = 0, not employed and not in the work force = 1).

greater than $25,000 per year were more likely to know that breast lumps could be a symptom of breast cancer (OR = 3.0, $P = .003$) and were less likely to believe that a woman needed a mammogram only when she had a breast lump (OR = 0.5, $P < .001$). When we evaluated Latinas alone, we found that a lower acculturation level was also a significant predictor of lower levels of knowledge and unfavorable attitudes about breast cancer (Table 4).

Discussion

The results indicated that Latinas, particularly those with lower acculturation levels, had less knowledge than Anglo women about risk factors and symptoms of breast cancer and had less desirable attitudes about the disease. For instance, Latinas were more likely to believe that medically unaccepted factors such as breast trauma, breast fondling, and multiple sexual partners increased the risk of breast cancer and were less likely to know that breast lumps and bloody breast discharge were symptoms. Moreover, they more often preferred not to know if they had breast cancer and would be afraid to tell their husbands. Of particular concern, Latinas were nearly twice as likely as Anglo women to believe that they only needed a mammogram when they had a breast lump.

This is the most extensive study to date on breast cancer-related knowledge and attitudes among Latinas. The results are consistent with those of previous investigations that reported lower levels of knowledge about cancer in general among Latinos.[18,19] Latinas' specific beliefs about breast cancer may reflect, in part, the moral framework within which they may interpret diseases. Indeed, Latinos often believe that cancer is God's punishment for improper or immoral behavior.[19] If sexual practices such as breast fondling or having multiple sexual partners increase the risk of breast cancer, then acquiring this disease may imply immoral behavior. Women may, therefore, be reluctant to learn that they have breast cancer and to inform their husbands about it.

The study had several limitations. First, although the cooperation rate of 78.5% was relatively high, we do not know if the women who declined to participate differed from respondents in their knowledge and attitudes about breast cancer. Second, the data come from self-reports and are subject to recall bias. Because the study primarily concerned knowledge and attitudes, however, this bias was of minor importance. Finally, the survey findings may not apply to families without telephones. Although households in Orange County have high telephone subscription rates (approximately 94% for Latinos and 99% for Anglos),[20] families without telephones have less access to medical care[21] and, therefore, may have less access to cancer-related information and less knowledge about breast cancer.

We conclude that Latinas' beliefs about breast cancer differ in important ways from those of Anglo women and that these beliefs may reflect the moral framework within which Latinas interpret diseases. The findings imply that breast cancer control programs should address these differences to provide more culturally sensitive interventions. The results may also help practicing physicians understand how patients with dissimilar cultural backgrounds respond to their medical recommendations. A better understanding of their patients' cultures is important in patient education and disease detection.

REFERENCES

1. Harris JR, Lippman ME, Veronesi U, Willet W: Breast cancer. N Engl J Med 1992; 327:319-328

2. Richardson JL, Langholz B, Bernstein L, Burciaga C, Danley K, Ross RK: Stage and delay in breast cancer diagnosis by race, socioeconomic status, age and year. Br J Cancer 1992; 65:922-926

3. Vernon SW, Tilley BC, Neale AV, Steinfeldt L: Ethnicity, survival, and delay in seeking treatment for symptoms of breast cancer. Cancer 1985; 55: 1563-1571

4. National Center for Health Statistics: National Health Interview Survey: United States 1987. Vital Health Stat [10] 1987, No. 118

5. Solis JM, Marks G, Garcia M, Shelton D: Acculturation, access to care, and use of preventive services by Hispanics: Findings from HHANES 1982-84. Am J Public Health 1990; 80(suppl):11-19

6. Access to Health Care in the United States: Results of a 1986 Survey—Special Report. Princeton, NJ, Robert Wood Johnson Foundation, 1987

7. Hubbell FA, Waitzkin H, Mishra SI, Dombrink J, Chavez LR: Access to medical care for documented and undocumented Latinos in a southern California county. West J Med 1991; 154:414-417

8. Bastani R, Marcus AC, Hollatz-Brown A: Screening mammography rates and barriers to use: A Los Angeles County survey. Prev Med 1991; 20:350-363

9. Race and Hispanic Origin, 1990 Census Profile. Washington, DC, Department of Commerce, Bureau of the Census, 1991

10. National Health Interview Survey Supplement Booklet Cancer Control. Washington, DC, Department of Commerce, Bureau of the Census, 1987

11. California Behavioral Risk Factor Survey, 1984-1989. Sacramento, Calif, Department of Health Services, 1989

12. Marin G, Sabogal F, Marin BV, Otero-Sabogal R, Pérez-Stable EJ: Development of a short acculturation scale for Hispanics. Hisp J Behav Sci 1987; 9: 183-205

13. Chavez LR, Hubbell FA, McMullin JM, Martinez RG, Mishra SI: Understanding knowledge and attitudes about breast cancer: A cultural analysis. Arch Fam Med 1994; 4:145-152

14. Bernard RH: Research Methods in Cultural Anthropology. Newbury Park, Calif, Sage Publications, 1988

15. Mishra SI, Dooley D, Catalano R, Serxner S: Telephone health surveys: Potential bias from noncompletion. Am J Public Health 1993; 83:94-99

16. Lemeshow S, Hosmer DW Jr: Estimating odds ratios with categorically scaled covariates in multiple logistic regression analysis. Am J Epidemiol 1984; 119:147-151

17. Simon R: Confidence intervals for reporting results of clinical trials. Ann Intern Med 1986; 105:429-435

18. A Study of Hispanics' Attitudes Concerning Cancer and Cancer Prevention. Atlanta, Ga, American Cancer Society, 1985

19. Pérez-Stable EJ, Sabogal F, Otero-Sabogal R, Hiatt RA, McPhee SJ: Misconceptions about cancer among Latinos and Anglos. JAMA 1992; 268: 3219-3223

20. US Bureau of the Census: 1990 Census of the Population and Housing, Summary Tape File 4. Sacramento, Calif, State Census Data Center, 1995

21. Corey DR, Freeman HE: Use of telephone interviewing in health care research. Health Serv Res 1990; 25:129-144

Articles

Use of Risk-Adjusted Outcome Data for Quality Improvement by Public Hospitals

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In 1993 the California Office of Statewide Health Planning and Development (OSHPD) began public release of risk-adjusted monitoring of outcomes (RAMO) under the California Hospital Outcomes Project. We studied how 17 acute care public hospitals in California used these RAMO data for quality improvement purposes following their initial distribution, first, by analyzing the outcome data for San Francisco General Hospital Medical Center as recommended by OSHPD and, second, by querying the departments at the other 16 public hospitals to determine how their own analyses compared. We found that the hospitals generally did minimal analyses of the OSHPD RAMO data and considered the data of little value to them. Only 3 hospitals initiated quality improvement activities based on their data review. The major reasons given by the hospitals for not using the RAMO data were that their outcomes were adequate, as verified by a comparison of their observed outcomes and those expected after risk-adjustment; that the hospitals had too few patients in the diagnostic categories; that they had too few resources; and that they were not concerned with the data's public release. Other possible explanations were that awareness of the California Hospital Outcomes Project was not widespread at the time of the study, that the RAMO data were not distributed in a way that encouraged their use, and that public hospitals were not inclined to use the outcome data because the project was imposed on them. Whatever the explanation, our study suggests that the California Hospital Outcomes Project has had little effect on quality improvement in public hospitals.

(Luce JM, Thiel GD, Holland MR, Swig L, Currin SA, Luft HS: Use of risk-adjusted outcome data for quality improvement by public hospitals. West J Med 1996; 164:410-414)

Risk-adjusted outcome data are commonly used to assess the quality of a hospital in response to external review or for improving performance internally.[1-5] In California, hospital discharge data collected by the Office of Statewide Health Planning and Development (OSHPD) are used under the California Hospital Outcomes Project to accomplish risk-adjusted monitoring of outcomes (RAMO).[6] The first report of the California Hospital Outcomes Project contained OSHPD discharge data from 1988 to 1990 and was publicly released in the fall of 1993. Included were one medical outcome, in-hospital mortality of patients with acute myocardial infarction, and two surgical outcomes, complications and lengths of postoperative stays for patients with cervical and lumbar discectomy. Cesarean section rates were considered for inclusion as an obstetrical outcome, but after a decision was made to study all methods of delivery, the obstetrical portion of the first report was postponed.[7]

In the first California Hospital Outcomes Project report, outcomes that were significantly better than expected or not better than expected were highlighted for public release of the RAMO data. Hospitals could determine if their outcomes were worse than expected by analyzing the data for their institutions, and this information was available to others who analyzed the report. In addition, two different models were used to adjust for patient differences among hospitals. The first employed only medical conditions likely to be present before hospital admission. The second model included these conditions and other diagnoses, such as shock, that might either have developed after admission or have been present at admission, in addition to social characteristics such as race and health insurance status. These last variables were thought to have substantial potential for altering the risk estimates at public hospitals.

In June 1993, California hospital chief executive officers received from OSHPD a draft of the first report of the California Hospital Outcomes Project that contained their facilities' RAMO data in the two areas described. The hospitals were given 60 days to review the data and make comments about them for the report, which was

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ABBREVIATIONS USED IN TEXT

HCFA = Health Care Financing Administration
OSHPD = Office of Statewide Health Planning and Development
RAMO = risk-adjusted monitoring of outcomes

scheduled for public release in December of that year. The hospitals also were provided with diskettes containing the RAMO data formatted to supply information relevant to understanding the outcomes of individual patients, such as the dates of their admission, their comorbidities, and whether they were transferred to or from other hospitals. In a booklet distributed with the diskettes, OSHPD offered detailed instructions about how hospitals might use the information included on the diskettes and also analyze the medical records of the patients listed on the diskettes both to respond to public release of their outcomes and to assess and improve the quality of care of other patients in the diagnostic and procedural categories.

Shortly after the drafts of the first California Hospital Outcomes Project report were distributed, we did the following study of the use of RAMO data for quality improvement by acute care public hospitals in California. The study consisted of two parts. First, we analyzed the RAMO data for patients at one public hospital, San Francisco General Hospital, as recommended by OSHPD. Then, using this analysis as a standard, we compared how other public hospitals analyzed their own RAMO data and used this information to improve quality. We focused on public hospitals because they care for many Californians and because they are expected to have poorer patient outcomes and hence to have a greater need for quality improvement. We also hoped to provide OSHPD with information regarding the effects of the California Hospital Outcomes Project on public hospitals.

Methods

San Francisco General Hospital Analysis

The analysis of OSHPD RAMO data at San Francisco General Hospital was conducted by the hospital Quality Management Department (L.S., S.A.C., and J.M.L.) after the draft report was forwarded to the hospital in June 1993. The study was limited to a single outcome, mortality of patients with acute myocardial infarction, because cervical and lumbar discectomies are not commonly done at San Francisco General Hospital. The study followed seven sequential steps:

- Reviewing the overall mortality results for patients with acute myocardial infarction as distributed by OSHPD,
- Obtaining from the diskette provided by OSHPD for further analysis a list of patients who died following acute myocardial infarction,
- Evaluating the accuracy of the hospital's coding of the discharge data it provided OSHPD,
- Performing a medical records technician review of the records of patients who died of acute myocardial infarction,
- Performing a nurse review of the records,
- Performing a physician review of the records, and
- Discussing the results of the analysis with hospital administrators and medical leaders before recommending projects for quality improvement.

Statewide Public Hospital Study

In December 1993, after the San Francisco General Hospital analysis was complete and the first California Hospital Outcomes Project report was publicly released, we (J.M.L., G.D.T., and M.R.H.) wrote the administrator and medical directors of the quality management departments of 22 other acute care public hospitals that are members of the California Association of Public Hospitals and Health Systems and asked if they were willing to fill out a standardized questionnaire to provide demographic information and to determine how they had used the RAMO data relevant to their own hospitals. The directors were informed that in return for filling out the questionnaires, they would receive copies of the analysis that San Francisco General Hospital performed on its own OSHPD RAMO data regarding patients who died of acute myocardial infarction. The letter was followed by phone calls to the quality management directors. If the directors agreed to participate in the study, they were sent the questionnaires and asked to return them by mail.

The study questionnaire began with questions related to hospital demographics. To provide an index of hospital commitment to quality and improvement, the questionnaire asked at what level the hospital staff was trained in continuous quality improvement and the number of continuous quality improvement activities in the hospital, both graded on a scale of 0 to 5. The hospitals' overall resource allocation to continuous quality improvement was graded on a scale of 0 to 10, with 0 being "none" and 10 "a very great deal." To provide information about the hospital use of other risk-adjusted outcome data in the past, the questionnaire asked whether hospitals had previously reviewed Medicare mortality data from the Health Care Financing Administration (HCFA) and whether they reviewed the medical records of Medicare patients who died. The questionnaire offered several options to explain why hospitals did not use the HCFA data if this was the case. In addition, the questionnaire asked for the overall value of the HCFA data to the hospitals, both on a scale of 0 to 10, with 0 being "none" and 10 being "a very great deal."

To determine public hospitals' use of the RAMO data provided by OSHPD, the questionnaire listed the seven steps followed by San Francisco General Hospital. Performing all seven steps for patients with acute myocardial infarction would yield what was called a Quality Improvement Score of 7, and also performing all seven steps for patients with cervical and lumbar discec-

tomy would yield a total Quality Improvement Score of 14 (hospitals without enough patients in these categories for the RAMO data to be meaningful would yield proportionately lower maximum possible Quality Improvement Scores). The questionnaire provided the same possible explanations as with the question regarding the HCFA data and why the various steps were not undertaken by the hospitals. The questionnaire also asked for a list of any quality improvement activities that had been initiated as a result of the use of the OSHPD RAMO data. In addition, the questionnaire asked the hospitals how they would characterize the overall value of the data to them on a scale of 0 to 10, with 0 being "none" and 10 "a very great deal."

After their questionnaires were returned in January 1994, the quality management directors received a copy of San Francisco General Hospital's analysis. In July 1994, they received a follow-up query to assess whether their hospitals had used the analysis in making quality improvement changes. The follow-up query asked whether hospitals had reviewed the San Francisco General Hospital analysis. It then asked that the usefulness of the San Francisco General Hospital analysis be graded on a scale of 0 to 10, with 0 being "useless" and 10 "very useful." The query then asked whether hospitals had made improvement changes related or unrelated to the San Francisco General Hospital analysis and, if so, what the changes were.

After receipt of the study questionnaires and follow-up queries, we analyzed the results and calculated the public hospitals' Quality Improvement Scores. Then, from the detailed statistical tables provided by OSHPD in the first California Hospital Outcomes Project report, we determined the z score used by OSHPD to indicate whether individual public hospitals had significantly different-than-expected adverse outcomes and then computed aggregate z scores (a z value greater than 1.96 or less than -1.96 is statistically significant at $P < .05$). We also determined from the tables the P values used by OSHPD to indicate the probability that differences in observed and expected outcomes at individual hospitals were attributable to chance, with a P value of .05 or less indicating systematic nonchance variations.[7] These individual hospital outcomes were recorded because hospitals with worse-than-expected outcomes might have a greater incentive to improve quality and therefore might have initiated more quality improvement activities.

Results

San Francisco General Hospital Analysis

Review of the OSHPD RAMO data for San Francisco General Hospital revealed that of 82 patients with acute myocardial infarction, 12 died between July 31, 1990, and May 31, 1991. Of these, 11 died at the hospital and 1 patient died after transfer to another facility. The Quality Management Department found it difficult to identify the 11 patients who died at that facility using the OSHPD RAMO data because the patients' hospital medical record numbers and Social Security numbers were not provided by OSHPD. As a result, the patients had to be identified by date of death and other distinguishing characteristics from a list of all patients with acute myocardial infarction during the OSHPD analysis period. One of the patients listed by OSHPD as having died after admission for acute myocardial infarction was miscoded by the hospital and did not actually have a myocardial infarction. Two patients were incorrectly stated by the hospital to have been 115 years old although they were much younger; this was done because the patients' ages were not known at the time discharge data were sent to OSHPD, and the hospital coders knew they would not be asked by OSHPD for corrected data if they listed the patients' ages as less than 120 years. Although all patients with acute myocardial infarction were admitted through the emergency department, most were incorrectly coded as nonemergency admissions.

No patterns such as similar times or days of death were identified in patients who died. In addition, record reviews by medical record technicians, the head nurse of the Coronary Care Unit, and the medical director of the Coronary Care Unit failed to reveal problems in the quality of care of patients with acute myocardial infarction once they were admitted to San Francisco General Hospital. The only issue raised was the poor quality of documentation of events in the field by the paramedics. This issue was subsequently taken up by the Critical Care Committee of the medical staff at San Francisco General Hospital, which declined to pursue it further.

Statewide Public Hospital Study

A total of 19 acute care public hospitals agreed to participate in the study, including San Francisco General Hospital. Of those hospitals, 17 acknowledged receiving their OSHPD RAMO data and were included in the final analysis. These hospitals were for the most part medium (100 to 299 beds) or large (300 or more beds) and located in urban or suburban areas. Most of them (15) had academic affiliations. As shown in Table 1, the public hospitals as a whole had substantial involvement in continuous quality improvement training and activities and had made considerable resource allocations to quality improvement. As shown in Table 2, however, their use of HCFA Medicare mortality data and OSHPD RAMO data for quality improvement purposes was minimal, and the value of the data release to the hospitals was perceived as low. Furthermore, few if any quality improvement activities were initiated in response to the RAMO data. The reasons cited most often by the hospitals for not using either the HCFA or OSHPD data were "outcomes adequate," followed by "too few patients in the diagnostic categories," "too few resources," and "not concerned about public release of the data."

Seven hospitals offered recommendations to improve the usefulness of the California Hospital Outcomes Project. Two hospitals cited the need for coding validation to verify the accuracy of their data. Two hospitals

TABLE 1.—*Continuous Quality Improvement (CQI) Activities of Public Hospitals (n = 17)*

Level of staff trained in CQI (scale 0–5)	
Median	4
Range	0–5
Number of CQI activities (scale 0–5)	
Median	3
Range	0–5
CQI resource allocation (scale 0–10)	
Median	5
Range	0–7

also asked that they be given instructions on how to interpret risk-adjustment methods, and two questioned the methods' accuracy. One hospital asked that OSHPD "develop data which the public can understand. The data released were developed for a statistical-type person and left too much room for misunderstanding."

Eleven hospitals responded to the follow-up query regarding their use of the San Francisco General Hospital analysis of its own OSHPD data. Of the responding hospitals, nine reviewed the analysis. Only one hospital initiated any quality improvement changes based on its review, a medical record review of RAMO data. One hospital had begun physician reviews of complications of discectomy patients coded by its medical records department to ensure the accuracy of discharge data sent to OSHPD, but this change was initiated independently of the review of the San Francisco General Hospital analysis.

Regarding their outcomes, the hospital group results for mortality from acute myocardial infarction were not significantly higher or lower than expected using both risk-adjustment models ($z = 0.497$ and 0.796, respectively). No hospital, including San Francisco General Hospital, had significantly worse-than-expected mortality among patients with acute myocardial infarction using both risk-adjustment models. The hospital group results for complications after cervical and lumbar discectomy were not worse than expected using both risk-adjustment models ($z = 0.226$ and 0.544 and 0.122 and 0.583). One hospital had a worse-than-expected complication rate for patients with lumbar discectomy using both risk-adjusted models ($P = .05$ and .05), but this appeared to be due to the fact that the sole patient who underwent this procedure had a complication. One hospital had worse-than-expected lengths of stay following cervical discectomy using the first risk-adjustment model ($P = .011$), and one hospital had longer-than-expected lengths of stay after lumbar discectomy using both risk-adjustment models ($P = .006$ and .005). None of the hospitals with worse-than-expected outcomes initiated significantly more quality improvement activities than hospitals with better-than-expected or not-better-than-expected outcomes.

Discussion

This study showed that public hospitals in California made generally little use of the RAMO data provided by OSHPD in the first year after distribution of the data to the hospitals or in the seven months following their public release. Furthermore, the use of the data by public hospitals was not increased by informing them how San Francisco General Hospital analyzed its own RAMO data. In explaining why they did not use the OSHPD RAMO data, the study hospitals most often said that their outcomes were adequate, that they had too few patients in the diagnostic categories, and that they had too few resources to devote to using the data. "Adequate outcomes" was also the reason most frequently given by the hospitals to explain why they did not use their HCFA Medicare mortality data in previous years. It would appear from these responses that public hospitals were unlikely to invest their limited resources in data review and quality improvement projects when their outcomes were not better than expected and even worse than expected for patients in the categories under study.

Public hospitals in California and other states have traditionally not had to compete for patients because they are "providers of last resort" that care primarily for the poor, many of whom are uninsured. Given this situation, it might be argued that the hospitals have little incentive to improve quality and need not be concerned about poor outcomes. Alternatively, it might be argued that public hospitals are unlikely to attract patients by demonstrating outcomes that are better than expected. Yet, competition for patients, at least those with Medicaid (Medi-Cal in California) and Medicare has increased dramatically in recent years, and most public hospitals have made important moves to maintain, if not increase, their share of sponsored patients. Furthermore, most California public hospitals have made substantial investments in quality improvement, as documented in the study. Because of this, we think that the hospitals would have made more use of the OSHPD RAMO data

TABLE 2.—*Public Hospital Use of HCFA Mortality Data and OSHPD RAMO Data*

Hospital Use	*HCFA Mortality Data Release*	*OHPD RAMO Data Release*
Hospital review of data release		
Yes	13	16
No	4	1
Hospital medical record review for individual patients		
Yes	8	7
No	9	10
Value of data release to hospitals (scale 0–10)		
Median	4	3
Range	0–10	0–10
Hospital quality improvement score for OSHPD data review (scale 0–14)		
Median	NA	4.5
Range	NA	0–11
Quality improvement activities initiated	NA	3

HCFA = Health Care Financing Administration, NA = not applicable, OSHPD = Office of Statewide Health Planning and Development, RAMO = risk-adjusted monitoring of outcomes

if they had perceived that such use would have been important and productive to them.

One explanation for the hospitals' limited use of RAMO data that was not specifically sought in the study is that the study was performed in the initial years of the California Hospital Outcomes Project, a time when awareness of the project was not broad and when only better-than-expected or not-better-than-expected outcomes were highlighted in the project report. Indeed, the quality management departments at two public hospitals denied that their facilities had ever received the OSHPD RAMO data or heard of their existence, despite the fact that the data had been sent to all hospitals in California through their chief executive officers. Although the quality management departments may have been bypassed at these two hospitals, the fact that they did not attempt to secure their hospital specific data suggests a low level of knowledge about or interest in the data and their public release.

Another possible reason that the OSHPD RAMO data were not extensively used is that the data were not distributed in a way that encouraged their use. To protect patients' confidentiality, their hospital medical record and social security numbers were not provided to California hospitals by OSHPD in the Hospital Outcomes Project Report. As a result, San Francisco General Hospital and other facilities that wanted to review individual patients' records had to identify the patients by indirect means. In addition, many directors of quality management expressed confusion about the risk-adjustment method used by OSHPD, although the method was explained in detail in the booklet distributed with the RAMO diskettes. Such confusion could have created a disincentive for conducting detailed outcome analyses.

A third possible reason for the limited use of the OSHPD RAMO data relates less to specific deficiencies in the data release process than to a distrust of the risk-adjustment method and a reluctance to allow the release of their RAMO data on the part of public, and presumably private, hospitals in California and other states. Indeed, public and private hospitals' distrust and reluctance can be traced through the history of the California Hospital Outcomes Project.[6] At this writing, hospitals continue to resent the fact that they are required at their own expense to provide OSHPD with discharge data that can be used against them in the competitive medical marketplace.

Whether this resentment remains in the future has yet to be determined. The OSHPD has made several changes in the California Hospital Outcomes Project, such as including social security numbers so that hospitals can identify patients more readily. An obstetrical outcome, readmission for postpartum complications of patients following vaginal and caesarean section deliveries, has been added to the second report, which was scheduled for release in the fall of 1995. Most important, this and presumably other future reports will highlight hospital outcomes that are significantly worse than expected in addition to those that are better than expected and not better than expected. It is not clear that worse-than-expected outcomes will be due to problems in the discharge data presented to OSHPD, risk-adjustment of the outcomes, or quality problems at the hospitals. Resolving this issue will be crucial because public and purchaser interest in the RAMO data is likely to increase as more people learn about the California Hospital Outcomes Project and other quality "report cards."

REFERENCES

1. DesHarnais S, McMahon LF Jr, Wrobleski R: Measuring outcomes of hospital care using multiple risk-adjusted indexes. Health Serv Res 1991; 26:425-445

2. Williams R, Chen P: 1978 California Birth Cohort: Perinatal Statistics Organized by Hospital and Geographic Areas. Sacramento, University of California, 1981

3. Blumberg M, Birrs G: Risk-Adjusted 30-Day Mortality of Fresh Acute Myocardial Infarctions: The Technical Report. Chicago, Ill, Hospital Research and Educational Trust, 1989

4. Iezzoni LI, Hotchkin EK, Ash AS, Shwartz M, Macieman Y: MedisGroups data bases—The impact of data collection guidelines on predicting in-hospital mortality. Med Care 1993; 31:277-283

5. Blumberg M: Risk-adjusted health care outcomes—A methodological review. Med Care Rev 1986; 5:351-393

6. Johns L: Measuring quality in California. Health Aff (Millwood) 1992; 11:266-270

7. California Hospital Outcomes Project—Annual Report. Sacramento, Calif, Office of Statewide Health Planning and Development, Health and Welfare Agency, 1993

Articles

AIDS-Related Experiences of Primary Care Physicians in Rural California, 1995

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A telephone survey was conducted of primary care physicians in nonmetropolitan counties of California. In a random sample of those counties reporting fewer than 30 cases of the acquired immunodeficiency syndrome (AIDS) as of December 1994, all physicians in practice were called; in counties reporting from 31 to 150 cases of AIDS as of the same date, a 30% random sample was selected for interviewing. Completion rates were 82% in the smallest counties and 70% in the larger counties (overall 72%). Two thirds of physicians reported that they had seen a patient positive for the human immunodeficiency virus and were providing continuing care for the disease. In all, 60% of physicians had seen a patient with AIDS. In these counties, there were 653 primary care physicians and 873 patients living with AIDS. The proportion of physicians providing care to persons with AIDS was twice that reported in previous surveys done in Los Angeles, California. In the interval (1985-1994), there was a 20-fold increase in the number of AIDS cases in California. In the nonmetropolitan areas, the number of AIDS cases in late 1994 was 290 times that reported in 1985.

(Lewis CE: AIDS-related experiences of primary care physicians in rural California, 1995. West J Med 1996; 164: 415-418)

Since 1984, about every two years we have surveyed random samples of office-based primary care physicians for their experiences and practices relating to the acquired immunodeficiency syndrome (AIDS) in Los Angeles, California. Each of these telephone surveys has involved from 200 to 1,000 physicians, with completion rates ranging from 60% to 75%.[1-5] The results have documented the gradual increase in the proportion of these physicians caring for patients infected with the human immunodeficiency virus (HIV) from 10% in 1984[2] to 42% among graduates of United States medical schools and 20% of international medical graduates in 1994.[3] These studies also have revealed the presence of a substantial proportion of physicians (about a third) who have refused to accept HIV-infected but asymptomatic patients into their practice.[4] The refusal to provide care has been found to be more prevalent in international medical graduates, many of whom are the principal providers of care to those subgroups that are increasingly affected by the epidemic.[5]

Only one of these surveys involved the entire State of California.[2] It compared the AIDS-related experiences and knowledge of 1,000 physicians from four areas: Los Angeles, San Francisco, other metropolitan counties, and nonmetropolitan counties of the state. A recent merger of AIDS Education and Training Centers (AETCs) in California provided a stimulus to reexamine the experiences of primary care physicians in the rural areas of California as of mid-1995 and to do a needs assessment.

As of December 1985, there were 3,759 cases of AIDS reported from the 58 counties of California (AIDS Epidemiology, Office of AIDS, California Department of Health, personal communication); this had grown to 79,256 in December 1994, or a 21-fold increase in nine years.[6] At the beginning of 1986, 3 cases had been reported from the 27 nonmetropolitan areas; 923 were from the 29 metropolitan counties other than Los Angeles and San Francisco, with each of the 27 metropolitan counties reporting at least 1 case (Office of AIDS, oral communication, May 1995).

Methods

Based on the data available on the number of AIDS cases reported by each county in California to the state health department through December 1994, two groups of counties were created for the purpose of sampling and interviewing. The first (A) contained all nonmetropolitan counties (n = 18) that had reported fewer than 30 cases since the onset of the epidemic. The second (B) contained the additional 9 nonmetropolitan counties of the state; they reported from 31 to 150 cases during this same period. Group B also contained 8 smaller metropolitan counties reporting a similar number (31 to

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ABBREVIATIONS USED IN TEXT

AETC = AIDS Education and Training Center
AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus
UCLA = University of California, Los Angeles

150) of AIDS cases, for a total of 17 counties. The population of counties in group A ranged from 3,300 to 37,000, with an average of 22,120. In group B, the county populations ranged from 52,000 to 319,000, with an average of 137,000. As of June 1995, in the 21 metropolitan counties of the state (other than Los Angeles and San Francisco), the number of cases ranged from 315 to 6,319.

A list of all primary care physicians—general internists, family physicians, and general practitioners—in office-based practice in the counties of groups A and B was obtained using the American Medical Association Master List. To assess different aspects of the HIV-related experiences of these physicians, two sampling approaches were used. Of the 18 rural counties in group A, 6 were selected at random, and 100% of physicians in these 6 counties were scheduled for interviews (n = 47). Among the 17 counties in group B, a 20% random sample of physicians was chosen (n = 124).

The interview schedule contained many of the items included in the previous surveys. Letters were sent to all physicians in groups A and B encouraging their participation and offering a donation of $10 to the charity of their choice, or to them, as a token of appreciation for their participation. The survey was conducted by the University of California, Los Angeles (UCLA), Institute for Social Survey Research in April and May of 1995.

Results

A substantial proportion of the initial sample (n = 171) of physicians in both groups A and B was no longer in practice in the communities in which they were listed (n = 23, 13.4%). Most of them had retired, and some had moved from the area. Among those contacted, 82% of eligible practitioners in group A (27/33) and 70% in group B (81/115) completed interviews, for an overall response rate of 73%, or 108 of 148. Unless otherwise noted, results were remarkably similar in both groups. Of those interviewed, 12% were women, 85% were graduates of US medical schools, and 35% were from one of the five schools of the University of California. Physicians in both groups had been in practice for 12 years (median), and 62% had been in practice in the area at the time of the initial December 1985 report on the number of AIDS cases by counties.

In all but one of the nonmetropolitan counties in California, those physicians interviewed included at least one who had cared for HIV-infected patients. One county in group A, with a population of 3,300, had reported three cases of AIDS to the state health department by December 1995. Two of these persons had died, and the one physician interviewed in that county had not seen an HIV-infected patient. In all other counties in group A and in 15 of the 17 counties in group B, at least one interview was conducted with a physician providing care to HIV-infected patients. In fact, in 11 of the total of 23 counties where interviews were completed, all of the physicians interviewed reported seeing HIV-infected patients.

The AIDS-related experiences of these physicians are shown in Table 1. Two thirds had seen a patient who was HIV-infected, and more than 60% had served or were serving as the primary care providers of one or more of these patients. The vast majority of those with such patients indicated that the patients had progressed to AIDS.

When asked, "If a patient with HIV infection came to your office, either one you diagnosed or who came to you with that diagnosis, would you accept the patient for care or refer the patient to another physician?" all (100%) of those caring for patients with HIV infection and 37% of those not caring for such patients said they would accept the patient for care.

It has been suggested that a sexual history should include the following:

- Whether the patient has sexual intercourse;
- With men, women, or both;
- Number of partners;
- History of a sexually transmitted disease; and
- If any partners engaged in high-risk activities.

Less than 10% took such a history, and only 24% of those interviewed took a sexual history of their adult patients that included the number and sex of partners and history of a sexually transmitted disease.

Of the 108 physicians, 85 (79%) responded affirmatively to the question, "Do you think all HIV-positive persons should be reported to the state health department, just like AIDS patients?"

TABLE 1.—*HIV-Related Experiences of Physicians in California's Smaller Communities*

Experience	*Group A (n = 27)*	*Group B (n = 81)*	*Total (n = 108)*
Response rate, %	82	70	73
Have seen HIV+ patient, No. (%)	20 (74)	53 (65)	73 (68)
Have seen an AIDS patient, No. (%)	18 (67)	47 (58)	65 (60)
Serves as the primary care physician for an HIV+ patient, No. (%)	17 (63)	53 (65)	70 (65)
Have seen HIV+ patient in past 6 months, No. (%)	12 (44)	32 (40)	44 (41)
County populations	3,300-7,000	52,000-319,000	3,300-319,000
Ratio of living cases of AIDS to primary care physicians as of December, 1994, No./No.	26/33	847/620	873/653

AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, + = positive.

TABLE 2.—*Responses of Those Having and Not Having HIV-Positive (+) Patients in Mid-1995, %*

Question	HIV+ Patients: Have (n=70)	HIV+ Patients: Have Not (n=38)
Would accept HIV+ patients	100	37
% of all patients on whom a sexual history is taken, median	10	4*
Suggested testing to patients	100	93*
Have other patients who should be tested	56	34†
Interested in CME	62	46*

CME = continuing medical education, HIV = human immunodeficiency virus

*Not significant.
†$\chi^2 = 4.80$, $P < .05$.

Testing

Whereas 87% of physicians said one or more of their patients had asked to be tested, there was a significant difference in the reported requests from patients of those physicians providing care to HIV-positive patients (95%) and those who were not (71%; $\chi^2 = 8.88$, $P < .01$, with Yates' correction). Other differences between those with and without HIV-infected patients are shown in Table 2.

Education

Of the 108 physicians, 60 (56%) expressed an interest in further education about AIDS. They were asked in an open-ended question what forms this education should (preferably) take. The most common response was lectures (39 [65%]) and audiovisual materials (12 [20%]). Comments made by the physicians also revealed the nature of their practice. They included, "I don't have time to read" and "I can't possibly get away." One suggested a loose-leaf notebook for updating treatment information. Despite its availability in the state, no one mentioned the use of a "hot-warm" consultation telephone line.

Discussion

Historical data on the growth of the AIDS epidemic in California may serve to contrast its behavior in various areas of the state.

From December 1985 to December 1994, in the two major metropolitan areas of California,[6] a 12.5-fold increase in the number of cases occurred in San Francisco (1,490 to 18,488) and a 20-fold increase occurred in Los Angeles (1,352 to 27,886). In 1994, however, the number of cases in nonmetropolitan counties was more than 290 times that reported in 1985 (3 to 877). Growth in the number of AIDS cases reported has been somewhat slower in the smaller metropolitan counties of the state (917 to 25,347, a 27-fold increase).

The magnitude of these differential growth rates may be due to the relative rate of reporting (and diagnosis) in the early years of the epidemic, their relative position on the epidemic curve of growth, migration, or simply noncompliance with reporting requirements in the mid-1980s. The fact that almost 80% of those interviewed think HIV-positive tests should be reported to the state speaks against this last option. Earlier studies that focused on Los Angeles have indicated that perhaps 40% of all primary care physicians are involved in the care of HIV-infected patients, with perhaps another 20% saying they are willing to do so.[3-5] In the least populated counties of California, however, 67% of primary physicians are providing care, with another 20% saying they will if patients present themselves.

As shown in Table 1, in the group A counties, 26 AIDS patients were living at the end of 1994 in areas where 33 primary care physicians were in practice. In group B counties, the ratio of AIDS patients to primary care physicians was 847 to 620. This is in contrast to the Los Angeles area where there are 17,907 patients with AIDS and 4,097 office-based primary care physicians.

In less than two decades since the initial cases were reported in Los Angeles,[7] AIDS has now reached the most remote areas of California. Moreover, in contrast to the urban area of Los Angeles County where only 35% of primary care office-based physicians have seen these patients, almost twice as many (67%) similar practitioners in the nonmetropolitan areas of the state are providing care. Also, none of the factors observed in previous studies in Los Angeles served to differentiate those rural physicians who would or would not accept these patients: age, sex, or school of graduation (US or international).[2-5]

The limitations of the findings of this survey relate to the sites, the response rate (72%), and the veracity of physicians' reports. The state health department indicates that AIDS has been reported by all but one California county. Presumably the experiences reported by physicians in this survey reflect this distribution.

Only one other report of the HIV-related practice experiences of primary care physicians in rural areas has been published. In that report, a questionnaire was mailed to 132 members of the Vermont Academy of Family Physicians: 106 responded, 57% of whom said they were caring for an asymptomatic HIV-positive patient. In Vermont, a total of 232 cases of AIDS have been reported as of 1995, of whom 140 are still living.[8]

Why would small-town physicians be twice as willing to accept HIV-positive patients as those in a megalopolis? Perhaps this is because there are so few of them in any area, a limited number of colleagues are available to "refer" these persons to, and there is more stigma associated with being known as a "refuser of care." Perhaps it is related to differences in their willingness to accept the Hippocratic oath as more than a hollow exercise, or perhaps familiarity fails to breed contempt.

The quality of the sexual history taking by smaller community physicians was poor, but no worse than in metropolitan areas. Because detailed questions regarding the management of HIV-infected patients were not included, we can infer nothing about the quality of care provided from this survey. Also, this study provides practitioners' perspective; no information is available

from potential patients on the lack of access to care. Those providing care to HIV-infected patients were interested in more education, but their comments revealed the challenges facing those who would provide effective education that actively involves the learner.

Of our series of reports on the HIV-related experiences and attitudes of primary care physicians over the past decade, this is the most optimistic. But what will happen if these physicians retire early because of the frustrations they currently experience? Although their numbers may decrease, the number of HIV-infected persons seeking or requiring care will continue to grow. Clearly AIDS is not a disease of our urban areas; it has spread to the most remote areas of the Golden State and in all probability those of the entire United States.

In the early days of AIDS continuing medical education, as provided by the AETCs and funded by the Division of Medicine of the Health Resources and Services Administration, the emphasis was on the traditional lecture or grand rounds approach. More recently, clinical hands-on training has been emphasized.[9] With the recognition that 15 years into the epidemic, ocular and neurologic complications are developing that are known to be common, some AETCs, such as that at UCLA, have developed clinical training opportunities for office-based ophthalmologists and neurologists to treat these patients under the guidance of experts. To date, these sessions at UCLA have been oversubscribed.

Offering programs for rural primary care physicians through recently developed distance learning technologies would seem to be the next step, based on the data presented. This step may never be taken, however, because funding for all professional education related to AIDS is proposed for reduction or elimination in Congress. In the debates as to the worthiness of the segment of humanity affected, some of our political leaders have expressed negative opinions. The outcomes of these debates over funding will send a message to the American people.

REFERENCES

1. Lewis CE, Freeman HE, Kaplan SH, Corey CR: The impact of a program to enhance the competencies of primary care physicians in caring for patients with AIDS. J Gen Intern Med 1986; 1:287-294

2. Lewis CE, Freeman HE, Corey CR: AIDS-related competence of California's primary care physicians. Am J Public Health 1987; 77:795-799

3. Lewis CE, Carlisle D: Continuing medical education about AIDS—A needs assessment. West J Med 1994; 161:34-38

4. Lewis CE, Montgomery K: Primary care physicians' refusal to care for patients infected with the human immunodeficiency virus. West J Med 1992; 156: 36-38

5. Lewis CE, Montgomery K: The AIDS-related experiences and practices of primary care physicians in Los Angeles: 1984-1989. Am J Public Health 1990; 80:1511-1513

6. California HIV/AIDS Update, 1995; 8:1-16

7. Gottlieb MS, Schroff R, Schanker HS, et al: *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: Evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981; 305:1425-1431

8. Gleeson CJ, Havron A, Wadland WC: Family physician management of HIV and AIDS: A Vermont study. J Fam Pract 1994; 39:50-54

9. Macher A, Goosby E, Barker L, et al: Educating primary care providers about HIV disease: Multidisciplinary interactive mechanisms. Public Health Rep 1994; 109:305-310

Articles

Role of Nitric Oxide in Progression and Regression of Atherosclerosis

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This article is based on a paper presented at the annual meeting of the Western Association of Physicians in Carmel, California, February 1995.

Endothelium-derived nitric oxide is a potent endogenous vasodilator that is derived from the metabolism of L-arginine. This endothelial factor inhibits circulating blood elements from interacting with the vessel wall. Platelet adherence and aggregation as well as monocyte adherence and infiltration are opposed by this paracrine substance. By virtue of these characteristics, endothelium-derived nitric oxide inhibits atherogenesis in animal models and may even induce regression.

(Cooke JP: Role of nitric oxide in progression and regression of atherosclerosis. West J Med 1996; 164:419-424)

The endothelium of the blood vessel wall is a diaphanous tissue only one cell layer thick. Despite its delicate appearance, the endothelium is a potent regulator of vascular tone and structure by virtue of the panoply of paracrine factors it produces. One of these paracrine substances is endothelium-derived relaxing factor (EDRF). The seminal article reporting the discovery of EDRF was published in 1980 by Furchgott and Zawadski, who speculated that it was a prostanoid metabolite of lipoxygenase.[1] Endothelium-derived relaxing factor is now known to be nitric oxide (NO).[2,3] In physiologic conditions, this molecule has a short half-life (measured in fractions of a second) unless it is bound to a carrier molecule, such as a thiol. Indeed, evidence indicates that EDRF may be released in the form of a nitrosothiol.[4] Nitric oxide is derived from the activity of the enzyme NO synthase, which oxidizes L-arginine to yield L-citrulline and NO.[5] Nitric oxide is the most potent endogenous vasodilator known and exerts its actions in the same manner as other nitrovasodilators such as nitroglycerin.[6] The NO moiety of nitrovasodilators activates soluble guanylyl cyclase within the vascular smooth muscle, leading to the production of cyclic guanosine monophosphate (cGMP). This cyclic nucleotide is the second messenger for the action of NO, and it activates cGMP-dependent proteins that mediate vascular smooth muscle relaxation.

Nitric oxide is released when specific receptors on the endothelium are occupied by their respective agonists, many of which circulate in the bloodstream. These agonists include thrombin and adenosine diphosphate released by aggregating platelets.[7-9] When the endothelium is intact, adenosine diphosphate and thrombin induce endothelium-dependent vasodilation. This response increases blood flow and inhibits the propagation of platelet thrombus. Nitric oxide also directly inhibits platelet reactivity.[10-13] Endothelium-derived NO and exogenous nitrovasodilators increase platelet cGMP, which has the effect of inhibiting platelet adherence and aggregation. There are also endothelial receptors for a number of vasoconstrictor substances such as serotonin, norepinephrine, vasopressin, and endothelin.[14,15] When the endothelial receptors are occupied by these agonists, NO is released, thereby attenuating the vasoconstriction to these agents. The endothelium tends to maintain vascular patency by halting the response to vasoconstrictors and by inhibiting platelet adherence and aggregation. In the presence of the endothelium, therefore, these vasoconstrictors cause mild vasoconstriction or even vasodilation; in the absence of a healthy endothelium, these agents act unopposed on the vascular smooth muscle, causing greater vasoconstriction. This is a homeostatic mechanism during traumatic arterial injury; the loss of endothelial influence facilitates platelet plug formation and vasoconstriction, thereby promoting hemostasis. This becomes a pathophysiologic mechanism when the endothelium is dysfunctional due to a systemic disorder (hyperlipidemia). Platelet adherence to the dysfunctional endothelium promotes thrombosis and the growth of vascular lesions.

The endothelium responds to physical forces and to humoral substances. As blood flow increases through a conduit vessel, the vessel increases in diameter.[16] This flow-mediated vasodilation requires the integrity of the

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ABBREVIATIONS USED IN TEXT

cGMP = cyclic guanosine monophosphate
EDRF = endothelium-derived relaxing factor
MCP-1 = monocyte chemotactic protein
NO = nitric oxide
NZW = New Zealand white [rabbits]

endothelium.[17] In most vessels, flow-mediated vasodilation is largely due to the release of endothelium-derived NO, although prostacyclin, endothelium-derived hyperpolarizing factor, and other substances may contribute in some circulations.[18-20] Flow-mediated vasodilation allows the vessel to accommodate to increases in blood flow and normalizes endothelial shear stress. The ability of the endothelium to sense and to respond to changes in flow allows the vessel to respond rapidly to local changes in hemodynamics. The signal transduction mechanism by which the endothelium senses and responds to flow is still poorly understood, but the cytoskeleton and specific ionic channels likely play a role.[21,22] Long-term increases in blood flow (such as with arteriovenous fistula or with regular exercise) increase the expression of endothelial NO synthase and are associated with an enhancement of endothelium-dependent relaxation.[23,24] The effect of ongoing exercise to enhance the expression of NO synthase may explain in part the reduction in vascular events incurred by persons partaking regularly of vigorous physical activity.[25]

Nitric Oxide—A Potent Inhibitor of Platelet and Leukocyte Reactivity

Nitric oxide is not only a potent vasodilator but has substantial effects on circulating blood elements. Like other NO donors, endothelium-derived NO inhibits platelet adherence and aggregation. After being incubated in vitro with endothelial cells, human platelets are less able to aggregate.[10,13] This effect persists even after the endothelial cells are pretreated with aspirin to inhibit their production of prostacyclin, a known antagonist of platelet reactivity. This persisting inhibition of platelet aggregation is due to the effects of endothelial-derived NO because the inhibition of platelet aggregation is associated with increases in platelet cGMP, and the effects of endothelial cells can be abolished by antagonists of NO action.

It has been shown experimentally that as platelets make one circuit through the coronary microvasculature, they are "conditioned" by the endothelium.[26] Platelet-rich plasma was administered to the coronary artery perfusate of an isolated Langendorf heart preparation. Subsequently, the platelets were collected in the coronary sinus effluent. When acetylcholine was added to the perfusate to stimulate the release of endothelium-derived NO, there was a substantial increase in cGMP in the platelets traversing the coronary microcirculation. Moreover, these platelets manifested diminished aggregatory responses to adenosine diphosphate as measured by platelet aggregometry. These effects could be blocked by coinfusion of NO-synthase antagonists. The data suggest that endothelium-derived NO released by the microvascular endothelium increases platelet cGMP and diminishes platelet reactivity.

In this way, normal endothelium suppresses platelet reactivity; dysregulation of the endothelium is likely associated with a greater tendency for platelet adherence and aggregation. Indeed, preliminary studies from our laboratory indicate that platelet aggregability is enhanced in hypercholesterolemic persons; this abnormal platelet reactivity can be reversed by the oral administration of the NO precursor L-arginine.

Nitric oxide also inhibits leukocyte adherence. This effect of NO was first observed in models of ischemia-reperfusion.[27,28] When the coronary artery of an experimental animal is ligated, this induces ischemia of the myocardium served by that vessel. When the ligature is released, the ensuing reperfusion is associated with a myocardial injury that is initiated by the adherence and infiltration of neutrophils and the concomitant release of oxygen-derived free radicals. The adherence of leukocytes and subsequent reperfusion injury can be markedly inhibited by the simultaneous perfusion of the coronary artery by sodium nitrite or other exogenous NO donors.[27,28] Alternatively, reperfusing the coronary artery with solutions containing the NO precursor (L-arginine) restores endogenous NO activity and also inhibits neutrophil adherence and infiltration.[29]

A profound influence of NO on leukocyte-vessel wall interactions has been observed in other experimental models. Using videomicroscopy, the "rolling" of leukocytes may be observed along the wall of small venules. This "rolling" represents a transient adherence of the leukocyte to the vessel wall due to the interaction of adhesion molecules and their ligands on the surface of the endothelium and the leukocyte. Occasionally the leukocytes become firmly adherent and infiltrate the vessel wall. When these small vessels are perfused with antagonists of NO synthase (to inhibit the elaboration of NO), the number of leukocytes that are rolling and those that become firmly adherent is greatly increased.[30] This increased activation of endothelial-leukocyte interaction can be reversed by perfusing the vessels with the NO precursor, L-arginine. These investigations suggest that NO is a potent modulator of leukocyte-vessel wall interactions. The mechanism by which NO inhibits leukocyte adherence and infiltration is under investigation. There is evidence that NO may inhibit the expression or activity of certain adhesion molecules or chemotactic proteins (or both) involved in these processes.[31,32]

Effects on Vascular Growth

Nitric oxide also modulates the growth of vascular smooth muscle cells. In vitro, NO donors inhibit the proliferation of vascular smooth muscle cells; this effect is mimicked by the exogenous administration of 8-bromo-cGMP, a stable analogue of the second messenger of NO action.[33] Other agents such as atrial natriuretic peptide that increase the intracellular levels of cGMP also inhibit

TABLE 1.—*Antiatherogenic Interventions—Association With Nitric Oxide Activity*

Intervention	*Example*
Angiotensin-converting enzyme inhibitors	Captopril
Calcium-entry antagonists	Diltiazem, nifedipine, verapamil, felodipine
HMG CoA-reductase inhibitors	Lovastatin
Antioxidants	Probucol, superoxide dismutase
High-density-lipoprotein cholesterol infusion	- -
Diet	Fish oil, arginine

HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A

the proliferation of vascular smooth muscle cells in culture.[34] Does NO inhibit the proliferation of vascular smooth muscle cells in vivo? Some initial studies indicate that it does indeed play an important role in controlling vascular growth. In a number of disease states where the release of NO is reduced or abolished, such as restenosis, hypercholesterolemia, and hypertension, there is an increase in the proliferation of vascular smooth muscle cells within the media and the intima. Evidence from our laboratory and others indicates that by augmenting the release of endogenous NO, vascular smooth muscle proliferation can be inhibited in these disease states. By experimentally enhancing vascular NO activity (by the oral administration of arginine or by the direct transfer of the gene for NO synthase into the vessel wall), myointimal hyperplasia is reduced after balloon angioplasty in experimental models of restenosis.[35-37]

Restoration of Nitric Oxide Activity in Vascular Disease

The proliferation of vascular smooth muscle cells, monocyte adherence and infiltration, and platelet adherence and aggregation are key processes involved in atherogenesis. Because endothelium-derived NO inhibits each of these processes, we have proposed that NO is an endogenous antiatherogenic molecule.[38,39] Therefore, atherogenesis would be promoted by an endothelial injury or alteration that results in a reduction in NO activity (such as that which occurs in hypercholesterolemia).

If a reduction in NO activity promotes atherogenesis, a restoration of NO activity might be expected to retard the progression of the disease.

Endothelial Dysfunction Is Reversible

We reasoned that if we could increase the synthesis of NO by vessel walls, a number of key processes in atherosclerosis would be inhibited and progression of the disease halted. We first showed that the endothelial dysfunction induced by hypercholesterolemia could be reversed by the administration of the NO precursor, L-arginine.[40-42] New Zealand white (NZW) rabbits were fed normal chow or a high-cholesterol diet. After eight weeks, the animals received an intravenous infusion of L-arginine or an excipient (normal saline solution) over one hour. After the infusion, NO-dependent vasodilation of the hindlimb resistance vessels was stimulated by intra-arterial infusions of acetylcholine (which stimulates muscarinic receptors on the endothelium to release NO). As expected, NO-dependent vasodilation in the hypercholesterolemic animals receiving normal saline solution was more inhibited than in animals fed a normal diet. By contrast, hypercholesterolemic animals receiving the L-arginine infusion demonstrated normal NO-dependent vasodilation.[40] Subsequently, thoracic aortas were harvested from these animals for studies of NO-dependent vasodilation in vitro. Vascular rings of thoracic aortas from hypercholesterolemic animals relaxed normally to the endothelium-independent vasodilator nitroglycerin. By contrast, NO-dependent vasodilation to acetylcholine was inhibited in the hypercholesterolemic animals receiving the saline infusion, but normalized in those animals receiving the infusion of L-arginine.[41]

We confirmed these observations in hypercholesterolemic humans.[42] Previously we had demonstrated an endothelial dysfunction in the forearm resistance vessels of otherwise healthy young humans with hypercholesterolemia.[43] We assessed endothelium-dependent and endothelium-independent vasodilation of the forearm vasculature using plethysmography. Intra-arterial infusions of sodium nitroprusside increased forearm blood flow in normal and hypercholesterolemic subjects to the same degree. By contrast, vasodilation was reduced in hypercholesterolemic humans in response to intra-arterial methacholine (which stimulates the release of endothelium-derived NO). The methacholine response became normal following the infusion of L-arginine. The effects of L-arginine were likely due to its metabolism to NO, because its effects are not mimicked by D-arginine (which is not a substrate for NO synthase). We have observed similar beneficial effects of L-arginine infusions in reversing the endothelial dysfunction associated with transplantation atherosclerosis.[44] Moreover, arginine does not alter endothelium-independent responses in hypercholesterolemic animals or humans.

The restoration of endothelium-dependent vasodilation by arginine may be caused by an enhanced synthesis of NO. This implies that hypercholesterolemia induces an abnormality in the enzyme NO synthase, an impairment in arginine transport, or an alteration in arginine metabolism by other intracellular pathways. Alternatively, arginine may have an indirect effect (such as reducing NO degradation by superoxide anion). This last mechanism, however, would not explain our observation that the ex vivo generation of nitrogen oxides is increased in the thoracic aorta of hypercholesterolemic animals receiving dietary arginine (discussed later).

Evidence That Nitric Oxide Inhibits Atherogenesis

Having shown that vascular NO activity could be normalized in persons and animals with hypercholesterolemia, we then postulated that a sustained improve-

Figure 1.—After 10 weeks of a 0.5% cholesterol diet, 40% of the surface area of the thoracic aorta of New Zealand white rabbits was involved by intimal lesions (**arrows; A**). In contrast, in animals fed a high-cholesterol diet supplemented with dietary arginine, surface area of the lesions was reduced by 75% (**B**) (from Cooke et al[38]).

ment in NO release would inhibit atherogenesis.[38,45] This hypothesis was supported indirectly by previous observations that all known agents that suppressed atherogenesis also enhanced NO-dependent vasodilation, where this had been assessed (Table 1). To test this hypothesis, we placed NZW rabbits on a normal or high-cholesterol diet; some of the animals on the high-cholesterol diet also received a sixfold increase in dietary arginine (or methionine, to control for changes in nitrogen and caloric balance). The supplemental dietary arginine did not alter the lipid profile nor any hemodynamic values in the hypercholesterolemic animals; the only difference between the hypercholesterolemic groups was that plasma arginine levels were doubled in the animals receiving dietary arginine. At ten weeks, the thoracic aorta and coronary arteries were harvested for studies of vascular reactivity and histomorphometry. In vitro, the contractions to norepinephrine were not different between groups (there are no adrenergic receptors on the endothelium of rabbit thoracic aortas; the effect of norepinephrine on the vessel wall is mediated solely by α_1-adrenergic receptors on the vascular smooth muscle). There was also no difference between groups in endothelium-independent relaxations to sodium nitroprusside. As expected, NO-dependent vasodilation to acetylcholine was inhibited in the hypercholesterolemic animals receiving the excipient. By contrast, hypercholesterolemic animals receiving L-arginine had an improvement in NO-dependent vasodilation to acetylcholine.

The improvement in vascular NO activity had a striking effect on vascular structure. Lesion surface area was reduced by about 75% in the thoracic aortas from hypercholesterolemic animals (Figure 1).[38] In the coronary arteries, lesions were observed in all hypercholesterolemic animals receiving the excipient, but were pristine in those hypercholesterolemic animals receiving arginine.[45]

We are investigating the mechanism of this striking antiatherogenic effect of NO. It appears to be due in part to the effect of endogenous NO to inhibit monocyte adherence to the endothelium in hypercholesterolemic animals.[46] We have observed that after only two weeks of a high-cholesterol diet, the thoracic aorta of hypercholesterolemic animals has increased adhesiveness for mononuclear cells, as demonstrated by a functional binding assay in vitro. Segments of thoracic aorta are placed in culture medium and incubated with monocytoid cells or with mononuclear cells isolated from the blood of normocholesterolemic rabbits. After 15 minutes, nonadherent cells are washed away with fresh medium and the number of bound cells enumerated using videomicroscopy. Substantially more monocytes adhere to the thoracic aortas from hypercholesterolemic rabbits (a threefold increase in the number of adherent cells). The number of adherent cells is reduced in thoracic aortas from hypercholesterolemic animals receiving dietary arginine. This is associated with an increase in the release of NO from these tissues. By contrast, when nitroarginine (an antagonist of NO synthase) is administered to animals with normal cholesterol levels, the number of adherent cells is dramatically increased. Thus, reductions in NO activity by hypercholesterolemia, or the inhibition of NO synthesis, is associated with increased monocyte-endothelial cell binding.

This effect of NO on endothelial adhesiveness for monocytes is likely due to its inhibition of adhesive glycoproteins or chemokines mediating endothelial-monocyte interaction. Accumulating evidence indicates that hypercholesterolemia imposes an oxidative stress on endothelial cells. This alteration in the endothelial redox state activates specific transcriptional pathways that induce the expression of oxidant-responsive genes.[47] These genes encode proteins such as vascular cell adhesion molecule (VCAM-1) and monocyte chemotactic protein (MCP-1), molecules that mediate monocyte binding to the endothelium. We postulate that endothelium-derived NO interferes with the activation of these transcriptional pathways by modulating the endothelial redox state. Nitric oxide is known to suppress the elabo-

ration of oxygen-derived free radicals by neutrophils, probably by inactivating oxidative enzymes that generate superoxide anion.[48] Nitric oxide likely exerts an inhibitory effect as well on endothelial oxidative enzymes. We and others have found that hypercholesterolemia causes endothelial cells to generate superoxide anion[49]; this effect of hypercholesterolemia can be mimicked by antagonism of NO synthase[50] and can be suppressed by exogenous NO donors or by the enhancement of endogenous NO activity.[51] Our preliminary studies in cell culture and in vivo reveal that the effect of NO to suppress endothelial generation of superoxide anion is associated with a decrease in NFκB-mediated expression of MCP-1 and a parallel suppression of monocyte binding to the endothelium.

Regression and Progression—Dependency on Nitric Oxide

At this point, we had found that by enhancing vascular NO activity we could suppress the development of atherogenesis. An important question remained unanswered, however: in the presence of preexisting endothelial dysfunction and vascular disease, can the administration of arginine restore NO activity and slow the progression of disease (or even induce regression)?

We have performed preliminary studies to address this question.[51] We administered normal or high-cholesterol chow to NZW rabbits for ten weeks. At this time, 30% to 40% of the thoracic aorta is involved by lesions, and there is reduced NO activity, as manifested by attenuated endothelium-dependent relaxations. Arginine was then added to the 0.5% cholesterol diet of half of the animals. At 10, 14, 18, and 23 weeks into the experimental protocol, the thoracic aorta was harvested for studies of vascular reactivity and histomorphometry. Administering arginine restored NO activity in most animals at 14 and 18 weeks.[52] This effect was associated with an apparent regression of disease. By contrast, hypercholesterolemic animals receiving the excipient had a progression of disease. By 23 weeks, administering arginine was no longer enough to restore NO activity in most animals receiving supplementation: in these animals, lesion surface area progressed. In a few animals, however, administering dietary arginine maintained vascular NO activity at normal levels; these "responders" enjoyed continued regression. Preliminary studies indicate that these effects of NO may be mediated by the suppression of redox-sensitive transcriptional pathways activating MCP-1.

To conclude, restoring NO activity reduced monocyte adhesion and accumulation in the vessel wall. The explanation for the apparent regression remains undetermined, but may include either or both an effect of NO on the elaboration of chemokines and adhesion molecules mediating the influx of monocytes or the efflux of lipid-laden macrophages. Apoptosis of cells contributing to lesion growth is another mechanism by which NO could mediate lesion regression.

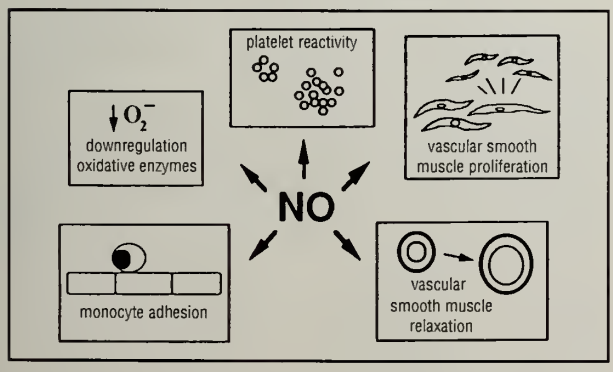

Figure 2.—Nitric oxide (NO) is an endogenous antiatherogenic molecule. In addition to being a potent vasodilator, it may inhibit a number of key processes in atherogenesis, including vascular smooth muscle proliferation, platelet adherence or aggregation, the generation of oxygen-derived free radicals, and monocyte adherence and infiltration (possibly by inhibiting the expression or activity of endothelial adhesion molecules or chemotactic proteins).

Summary

The cumulative data indicate that NO is an endogenous antiatherogenic molecule by virtue of its effects to inhibit monocyte adherence, platelet aggregation, and vascular smooth muscle proliferation (Figure 2). These salutary effects of NO may be mediated by its effect in modifying the endothelial redox state, as well as increasing intracellular cGMP levels. The impairment of NO activity by hypercholesterolemia, diabetes mellitus, or hypertension likely plays a role in the initiation of atherosclerosis. Recent insights into endothelial biology suggest a new paradigm for atherosclerosis, where modulation of the endothelial redox state plays a major role in the expression of genes related to atherogenesis. It is likely that these basic insights regarding mechanisms of atherogenesis will lead to new therapeutic strategies to halt the progression, or induce the regression, of atherosclerosis.

REFERENCES

1. Furchgott RF, Zawadski JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 268:373-376

2. Palmer RMJ, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987; 327: 524-526

3. Furchgott RF: Studies on relaxation of rabbit aorta by sodium nitrite: The basis for the proposal that the acid-activatable inhibitory factor from retractor penis is inorganic nitrite and the endothelium-derived relaxing factor is nitric oxide. *In* Vanhoutte P (Ed): Mechanisms of Vasodilation. New York, NY, Raven Press, 1988

4. Myers PR, Minor RL, Guerra R Jr, Bates JN, Harrison DG: Vasorelaxant properties of the endothelium-derived relaxing factor more closely resemble S-nitrosocysteine than nitric oxide. Nature 1990; 345:161-163

5. Palmer RMJ, Ashton DS, Moncada S: Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature 1988; 333:664-666

6. Ignarro LJ, Byrns RE, Buga GM, Wood KS: Endothelium-derived relaxing factor from pulmonary artery and vein possesses pharmacologic and chemical properties identical to those of nitric oxide radical. Circ Res 1987; 61:866-879

7. DeMey JG, Vanhoutte PM: Heterogeneous behavior of the canine arterial and venous wall: Importance of the endothelium. Circ Res 1982; 51:439-447

8. Cohen RA, Shepherd JT, Vanhoutte PM: Inhibitory role of the endothelium in the response of isolated coronary arteries to platelets. Science 1983; 221: 273-274

9. Houston DS, Shepherd JT, Vanhoutte PM: Adenine nucleotides, serotonin, and endothelium-dependent relaxations to platelets. Am J Physiol 1985; 248(pt 2):H389-H395

10. Radomski MW, Palmer RM, Moncada S: An L-arginine/nitric oxide pathway present in human platelets regulates aggregation. Proc Natl Acad Sci USA 1990; 87:5193-5197

11. Stamler JS, Mendelsohn ME, Amarante P, et al: *N*-acetylcysteine potentiates platelet inhibition by endothelium-derived relaxing factor. Circ Res 1989; 65:789-795

12. Mellion BT, Ignarro LJ, Ohlstein EH, et al: Evidence for the inhibitory role of guanosine 3′,5′-monophosphate in ADP-induced human platelet aggregation in the presence of nitric oxide and related vasodilators. Blood 1981; 57:946-955

13. Mellion BT, Ignarro LJ, Myers CB, et al: Inhibition of human platelet aggregation by S-nitrosothiols. Heme-dependent activation of soluble guanylate cyclase and stimulation of cyclic GMP accumulation. Mol Pharmacol 1983; 23:653-664

14. Cocks TM, Angus JA: Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. Nature 1983; 305:627-630

15. Katusic ZS, Shepherd JT, Vanhoutte PM: Vasopressin causes endothelium-dependent relaxations of the canine basilar artery. Circ Res 1984; 55:575-579

16. Hilton SM: A peripheral arterial conducting mechanism underlying dilation of the femoral artery and concerned in functional vasodilation in skeletal muscle. J Physiol (London) 1959; 149:92-111

17. Hull SS, Kaiser L, Jaffe MD, Sparks HV: Endothelium-dependent flow induced dilation of canine femoral and saphenous arteries. Blood Vessels 1986; 23:183-198

18. Cooke JP, Stamler JS, Andon N, Davies PF, Loscalzo J: Flow stimulates endothelial cells to release a nitrovasodilator that is potentiated by reduced thiol. Am J Physiol (Heart Circ Physiol) 1990; 28:H804-H812

19. Koller A, Kaley G: Prostaglandins mediate arteriolar dilation to increased blood flow velocity in skeletal muscle microcirculation. Circ Res 1990; 67: 529-534

20. Feletou M, Vanhoutte PM: Endothelium-dependent hyperpolarization of canine coronary smooth muscle. Br J Pharmacol 1988; 93:513-524

21. Oleson SP, Clapham DE, Davies PF: Haemodynamic shear stress activates a K+ current in vascular endothelial cells. Nature (London) 1988; 331:168-170

22. Cooke JP, Rossitch E, Andon N, Loscalzo J, Dzau VJ: Flow activates a specific endothelial potassium channel to release an endogenous nitrovasodilator (Abstr). J Am Coll Cardiol 1990; 15:1A

23. Miller VM, Vanhoutte PM: Enhanced release of endothelium-derived factor(s) by chronic increases in blood flow. Am J Physiol (Heart Circ Physiol 24) 1986; 251:H520-H527

24. Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH: Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. Circ Res 1994; 74:349-353

25. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Crique MH, Sheps DS: Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. N Engl J Med 1988; 319:1379-1384

26. Pohl U, Busse R: EDRF increases cyclic GMP in platelets during passage through the coronary vascular bed. Circ Res 1989; 65:1798-1803

27. Johnson G 3d, Tsao PS, Mulloy D, Lefer AM: Cardioprotective effects of acidified sodium nitrite in myocardial ischemia with reperfusion. J Pharmacol Exp Ther 1990; 252:35-41

28. Siegfried MR, Carey C, Ma XL, Lefer AM: Beneficial effects of SPM-5185, a cysteine-containing NO donor, in myocardial ischemia-reperfusion. Am J Physiol 1992; 263(pt 2):H771-H777

29. Weyrich AS, Ma XL, Lefer AM: The role of L-arginine in ameliorating reperfusion injury after myocardial ischemia in the cat. Circulation 1992: 86: 279-288

30. Kubes P: Ischemia-reperfusion in feline small intestine: A role for nitric oxide. Am J Physiol 1993; 264(pt 1):G143-G149

31. De Caterina R, Libby P, Peng HB, et al: Nitric oxide decreases cytokine-induced endothelial activation—Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest 1995; 96:60-68

32. Peng HB, Rajavashisth TB, Libby P, Liao JK: Nitric oxide inhibits macrophage-colony stimulating factor gene transcription in vascular endothelial cells. J Biol Chem 1995; 270:17050-17055

33. Garg UC, Hassid A: Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. J Clin Invest 1989; 83:1774-1777

34. Itoh H, Pratt RE, Dzau VJ: Atrial natriuretic polypeptide inhibits hypertrophy of vascular smooth muscle cells. J Clin Invest 1990; 86:1690-1697

35. McNamara DB, Bedi B, Aurora H, et al: L-Arginine inhihits balloon catheter-induced intimal hyperplasia. Biochem Biophys Res Commun 1993; 193:291-296

36. Tarry WC, Makhoul RG: L-Arginine improves endothelium-dependent vasorelaxation and reduces intimal hyperplasia after balloon angioplasty. Arterioscler Thromb 1994; 14:938-943

37. von der Leyen HE, Gibbons GH, Morishita R, et al: Gene therapy inhibiting neointimal vascular lesion: In vivo transfer of endothelial cell nitric oxide synthase gene. Proc Natl Acad Sci USA 1995; 92:1137-1141

38. Cooke JP, Singer AH, Tsao P, Zera P, Rowan RA, Billingham ME: Antiatherogenic effects of L-arginine in the hypercholesterolemic rabbit. J Clin Invest 1992; 90:1168-1172

39. Cooke JP, Tsao PS: Is NO an endogenous antiatherogenic molecule? Arterioscler Thromb 1994; 14:653-655

40. Girerd XJ, Hirsch AT, Cooke JP, Dzau VJ, Creager MA: L-Arginine augments endothelium-dependent vasodilation in cholesterol-fed rabbits. Circ Res 1990; 67:1301-1308

41. Cooke JP, Andon NA, Girerd XJ, Hirsch AT, Creager MA: Arginine restores cholinergic relaxation of hypercholesterolemic rabbit thoracic aorta. Circulation 1991; 83:1057-1062

42. Creager MA, Girerd XJ, Gallagher SJ, Coleman S, Dzau VJ, Cooke JP: L-Arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. J Clin Invest 1992; 90:1248-1253

43. Creager MA, Cooke JP, Mendelsohn ME, et al: Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. J Clin Invest 1990; 86:228-234

44. Drexler H, Fischell TA, Pinto FJ, Chenzbraun A, Cooke JP, Alderman EA: Effect of L-arginine on coronary endothelial function in cardiac transplant recipients: Relationship to vessel wall morphology. Circulation 1994; 89:1615-1623

45. Wang B, Singer A, Tsao P, Drexler H, Kosek J, Cooke JP: Dietary arginine prevents atherogenesis in the coronary artery of the hypercholesterolemic rabbit. J Am Coll Cardiol 1994; 23:452-458

46. Tsao P, McEvoy LM, Drexler H, Butcher EC, Cooke JP: Enhanced endothelial adhesiveness in hypercholesterolemia is attenuated by L-arginine. Circulation 1994; 89:2176-2182

47. Marui N, Offerman MK, Swerlick R, et al: Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression are regulated through an antioxidant-sensitive mechanism in human vascular endothelial cells. J Clin Invest 1993; 92:12866-12874

48. Clancy RM, Leszczynska-Piziak J, Abramson RB: Nitric oxide, an endothelial cell relaxation factor, inhibits neutrophil superoxide anion production via a direct action on NADPH oxidase. J Clin Invest 1992; 90:1116-1121

49. Ohara Y, Petersen TE, Harrison DG: Hypercholesterolemia increases endothelial superoxide anion production. J Clin Invest 1993; 91:2546-2551

50. Niu X, Smith CW, Kubes P: Intracellular oxidative stress induced by nitric oxide synthesis inhibition increases endothelial cell adhesion to neutrophils. Circ Res 1994; 74:113-114

51. Candipan RC, Wang BY, Buitrago R, Tsao P, Cooke JP: Regression or progression: Dependency on vascular nitric oxide. Arterioscler Thromb Vasc Biol 1996; 16:44-50

52. Tsao PS, Buitrago R, Chan JR, Cooke JP: Fluid now inhibits endothelial adhesiveness: NO and transcriptional regulation of VCAM-1. Circulation 1996, in press

Conferences and Reviews

Atrial Fibrillation

Pearls and Perils of Management

Discussant

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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. It has been edited by Scott Ramsey, MD, Chief Medical Resident; Henry Rosen, MD, Professor and Associate Chair; and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

Atrial fibrillation, a common arrhythmia, is responsible for considerable cardiovascular morbidity. Its management demands more than antiarrhythmic therapy alone, but must address the causes and consequences of the arrhythmia. Although remediable causes are infrequently found, a thorough search for associated heart disease or its risk factors results in better-informed patient management. Controlling the ventricular response and protecting from thromboembolic complications are important initial goals of therapy and may include the administration of aspirin in younger, low-risk patients. Older patients and those with risk factors for systemic embolism are not adequately protected from stroke complications by aspirin therapy alone. It remains controversial whether all high-risk patients should receive warfarin and at what intensity. Whether and how sinus rhythm should be restored and maintained poses the greatest therapeutic controversy for atrial fibrillation. The mortal risk of antiarrhythmic therapy is substantially greater in patients with evidence of heart failure. In such persons, the risks and benefits of maintaining normal sinus rhythm with antiarrhythmic medications should be weighed carefully. A definitive cure for atrial fibrillation remains elusive, but promising surgical and catheter ablation therapies are being developed.

(Kudenchuk PJ: Atrial fibrillation—Pearls and perils of management. West J Med 1996; 164:425-434)

Atrial fibrillation is the most common sustained arrhythmia encountered in clinical practice. It afflicts about 4% of the United States population, or more than 1.5 million people, is more common in men, and its prevalence rises sharply with increasing age (from 0.1% to 0.4% at ages 40 to 59 to 7% to 11.6% in those older than 70) and with overt evidence of other heart disease.[1-3] Paroxysmal atrial fibrillation is estimated to account for a third of all cases.[4] Since first described in 1903, atrial fibrillation has remained both a pathophysiologic enigma and a therapeutic challenge.* Electrophysiologically, it has been characterized as an irregular, disorganized atrial rhythm due to multiple simultaneously circulating reentrant waves, to which the ventricular response is irregular or random.[5,6] The heart's propensity to fibrillation may be related to an inhomogeneity in the electrical properties of myocardial cells. Fibrillation also requires a critical mass of tissue, which may in part explain why atrial fibrillation is rarely observed in the small hearts of animals such as rats or rabbits and is more common in larger mammals and humans.[7] Any number of conditions that result in increased atrial size or that alter atrial conduction or refractoriness (or both) can predispose to the development of atrial fibrillation.

Atrial fibrillation is a self-perpetuating arrhythmia. When repeatedly induced in animals, it becomes of successively longer duration.[8] In humans, atrial fibrillation appears to contribute to further atrial enlargement[9]; paroxysmal episodes of the arrhythmia frequently precede the chronic sustained form, and it has been observed that the longer the chronicity of the sustained form, the greater its resistance to remission with treatment.[10]

Atrial fibrillation has many causes, and its effects span multiple organ systems and medical disciplines. In addition to the host of symptoms that accompany the arrhythmia, atrial fibrillation reduces stroke volume and

*See also the editorial by F. Morady, MD, "Pulsus Irregularis Perpetus—100 Years of Progress, But Many Issues Still Unresolved," on page 451 of this issue.

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
SPAF = Stroke Prevention in Atrial Fibrillation [trial]

cardiac output[11,12] and substantially increases the risk of stroke. Although not usually considered a dangerous arrhythmia, it can lead to life-threatening consequences if treated inappropriately. Managing such a complex rhythm entails addressing four central questions:

- Is there a remediable cause?
- Is the heart rate (ventricular response) adequately controlled?
- Is anticoagulation necessary?
- Can and should normal sinus rhythm be restored?

Remediable Causes of Atrial Fibrillation

Atrial fibrillation often occurs as an expression of focal or systemic illness or the consequence of an environmental exposure, such as to alcohol or other drugs. As such, this disorder is best viewed not as a final diagnosis, but as the presentation of an underlying disorder that merits a thorough investigation. With the decline of rheumatic valvular heart disease, atrial fibrillation is now most commonly observed in patients with hypertensive and ischemic heart disease and congestive heart failure.[13] Unless accompanied by signs or symptoms of active ischemia, however, atrial fibrillation is rarely the manifestation of a "silent" acute ischemic event or myocardial infarction.[14] Noncardiac causes include other chest disorders (exacerbated obstructive lung disease, pneumonia, pulmonary embolism, and following a thoracic operation),[15] endocrinologic problems (hyperthyroidism and pheochromocytoma),[16] and intoxicants (alcohol-related holiday heart syndrome or stimulant-drug abuse). Bradycardia has been noted to predispose to atrial fibrillation, suggesting a possible role of the parasympathetic nervous system in the development of the arrhythmia.[17,18] The sympathetic nervous system has also been implicated as a cause when atrial fibrillation is observed in the context of high catecholamine tone, such as with substance abuse or postoperatively.

Independent risk factors for atrial fibrillation developing were recently determined from a nearly 40-year follow-up of 4,731 patients who made up the original cohort of the Framingham Heart Study.[19] The likelihood of atrial fibrillation developing was 1.5 times higher in men than in women, independent of other risk factors such as age, smoking, diabetes mellitus, left ventricular hypertrophy, or ischemic and valvular heart disease. Each advancing decade of age approximately doubled the risk of the arrhythmia developing in both sexes. In both men and women, diabetes mellitus, hypertension, congestive heart failure, and valvular heart disease independently contributed to the occurrence of atrial fibrillation.

In a few patients (<3%), no apparent structural heart disease or disease process accompanies the arrhythmia.[20] So-called lone atrial fibrillation is a diagnosis of exclusion and implies primary electrical disease of the atria.[21] Atrial fibrillation in the absence of a clear cause may also suggest the presence of an accessory pathway. Patients with either overt Wolff-Parkinson-White syndrome or concealed accessory bypass tracts have a higher-than-expected incidence of atrial fibrillation.[22] In the context of an accessory pathway, the ventricular rate response to the arrhythmia may be rapid enough to be acutely life-threatening. Careful review of the electrocardiogram and ambulatory monitoring for the detection of preexcitation or arrhythmia patterns that suggest the presence of an accessory pathway is merited in patients with paroxysmal atrial fibrillation of unknown cause. Even in the absence of overt preexcitation, isolated episodes of regular paroxysmal supraventricular tachycardia (with or without spontaneous degeneration to atrial fibrillation) in a patient with otherwise unexplained paroxysmal atrial fibrillation suggest the presence of a "concealed" accessory pathway.[23] Ablation of the accessory pathway can possibly cure the patient of both paroxysmal supraventricular tachycardia and atrial fibrillation.[24,25]

The frequent association of this disorder with other, often even more serious, disorders makes treatment of the arrhythmia no less important than identifying and treating the "bad company" that it keeps. Even if a remediable cause is not found, treating atrial fibrillation in the context of the underlying disease results in better patient management. Finally, if risk factors that contribute to the incidence of both structural heart disease and the arrhythmia can be identified and modified at an early stage, it may even be possible to prevent the disorder altogether.

Rate Control

Achieving control of the ventricular rate in atrial fibrillation is an essential initial goal of management. The ventricular rate in this disorder is largely determined by the degree to which the rapid atrial impulses of random origin, strength, and sequence may bombard the atrioventricular (AV) node but fail to consistently conduct to the ventricle. Atrioventricular node function can be compared to a "filter" that allows the passage of impulses only after a prespecified time (the refractory period) has transpired since a previous impulse was permitted entry through the node. The refractory period of the AV node prolongs progressively at faster atrial rates, affording even fewer impulses the right of passage to the ventricle. In addition, impulses that partially enter the node but fail to conduct entirely through to the ventricle may nonetheless alter the upper margins of the node and impair the passage of subsequent impulses—"concealed conduction."[26]

A rapid ventricular rate associated with hemodynamic instability or symptoms of myocardial ischemia renders atrial fibrillation a medical emergency. This event demands immediate measures to slow or terminate the arrhythmia, usually with electrical cardioversion. If not hemodynamically compromising, pharmacologic methods are initially used to control the rate. First-line therapy in these circumstances is the use of digoxin and

β- and calcium channel blockers, all of which principally act to slow conduction through the AV node.

Although treatment with digoxin is time-honored, it seldom achieves rapid or adequate rate control, particularly in the acute stage and even with intravenous administration. Unlike its direct inotropic action,[27] the rate-slowing effect of digoxin is indirect and mediated principally by enhanced parasympathetic tone.[28,29] Digoxin, through enhanced parasympathetic tone, increases AV node refractoriness, which decreases the proportion of impulses that can be conducted through to the ventricle. Digoxin's other, less appreciated, vagally mediated effect on myocardium is to shorten tissue refractoriness. This effect results in an even more rapid atrial rate,[30] yet, paradoxically, accounts for another mechanism by which digoxin slows the ventricular response in atrial fibrillation. With more rapid bombardment by atrial impulses, the refractory period of the AV node and the degree of concealed conduction increase, resulting in a slower ventricular rate.[31]

That digoxin acts by enhancing parasympathetic tone to slow the ventricular rate explains its delayed onset of action and paucity of effect under certain conditions. Digitalis effect can be counteracted by a reversal of parasympathetic tone with the administration of atropine sulfate.[32] Similarly, in the presence of heightened sympathetic (and diminished parasympathetic) tone, digoxin therapy is unlikely to achieve an important reduction in heart rate. Thus, if under the circumstances the heart rate is likely to remain tachycardic even if a sinus rhythm were restored, the clinical response to digoxin will be poor.

Because of its positive inotropic properties, digoxin is the drug of choice for treating atrial fibrillation in patients with congestive heart failure. Efforts should also be concurrently directed at lowering the sympathetic tone by primary treatment of the heart failure, so as to diminish "sympathetic resistance" to the digoxin effect. When the sympathetic nervous system tone is high, attempts to overcome rapid atrial fibrillation with escalating doses of digoxin will result in toxicity long before the rate is controlled. Agents with more potent and direct AV node-blocking properties, such as β- or calcium channel blockers, are more likely to control the heart rate, but unlike with the use of digoxin, their use is precarious when cardiac function is substantially impaired. On occasion, combining the use of full-dose digoxin and carefully titrated doses of diltiazem obtains a higher degree of rate control with less risk of worsened heart failure than the use of either agent alone.

The use of antiarrhythmic agents as primary therapy for acute atrial fibrillation should be reserved for special circumstances. One such circumstance is when rate control remains unsatisfactory and the heart will not tolerate the negative inotropic effects of β- or calcium channel blockers. Primary antiarrhythmic agents such as procainamide can be used along with digoxin in an effort to slow the ventricular rate. Such use has important associated risks related to the conversion of atrial fibrillation to normal sinus rhythm before adequate time for anticoagulation has transpired, as well as to the provocation of ventricular arrhythmias, particularly in a patient with decompensated heart failure. Another acute circumstance in which a primary antiarrhythmic drug may be the first therapeutic agent of choice is when atrial fibrillation arises in patients with known Wolff-Parkinson-White syndrome.[33] Accessory pathway conduction is at best not altered and may even be accelerated to extremely rapid ventricular rates by digoxin or β- or calcium channel blockers. The use of any drug whose principal action is to slow conduction across the AV node is dangerous and contraindicated when atrial fibrillation arises in these patients.[34-36]

Although a major focus of therapy in patients with acute atrial fibrillation, heart rate control is largely neglected in the long-term management of this disorder. All too commonly, clinicians are falsely reassured by heart rates that appear controlled at rest but may climb uncontrollably when not being scrutinized during high sympathetic states, such as periods of stress and exercise.[37] Excessively rapid heart rates shorten the diastolic filling period, resulting in diminished stroke volume and cardiac output, and are a major contributor to symptoms imposed on patients by stress or exercise. Unless patients are evaluated during exercise or activities of daily living, treatable symptoms related to excesses of heart rate may be incorrectly ascribed to cardiac inefficiency from loss of AV synchrony.

A second and perhaps even more important reason for confirming the adequacy of rate control in the chronic phase of atrial fibrillation is its possible contribution to chronic cardiac dysfunction. Tachycardia-mediated cardiomyopathy has been well described in patients with incessant forms of supraventricular tachycardia, but has only recently been identified in patients with atrial fibrillation.[38-40] In one such report, the left ventricular ejection fraction was observed to double—from a median of 0.25 to 0.52—over the course of weeks to months in patients in whom, regardless of sinus rhythm being restored, rates were successfully slowed, only to deteriorate later when heart rates again rose uncontrollably.[41] Thus, the benefits of long-term rate control may be measured not only by a lessening of symptoms, but also by the preservation of left ventricular function.

To obtain optimal long-term rate control may require the addition of β- or calcium channel blocking agents, particularly when digoxin is otherwise used as primary therapy.[42] Defining a precise numeric range for rate control (an optimal target heart rate) in patients with atrial fibrillation is controversial because the benefits of a longer diastolic filling period and higher left ventricular stroke volume achieved with a lower heart rate may be offset by an overly diminished cardiac output from too-few beats per minute. Conversely, faster heart rates may compromise diastolic filling and stroke volume, thereby diminishing cardiac output. A "controlled" ventricular

rate in atrial fibrillation can be operationally defined as that which affords achieving maximum cardiac output with activity and yet does not compromise cardiac output at rest. By this definition, given the possible loss of cardiac efficiency from the fibrillation itself and the beat-to-beat variability in stroke volume and contractility, it has been suggested that cardiac output may be optimal at rest with a ventricular rate of 90 beats per minute[43] and, by extrapolation, during activity at rates that are as much as 20% to 50% faster than if in sinus rhythm.

In the case of drugs such as digitalis or β- or calcium channel blockers, whose principal effect is to slow conduction through the AV node, it is commonly presumed that their use will promote the restoration of normal sinus rhythm or, once restored, ensure its preservation. None of these drugs have intrinsic antiarrhythmic properties that would promote the restoration of normal sinus rhythm. In a prospective, randomized, double-blind evaluation of the use of digoxin versus placebo for acute atrial fibrillation, conversion to sinus rhythm was as successful with the use of placebo as it was with digoxin.[44] Similarly, in trials in which digoxin has been used with and without other antiarrhythmic agents for the prevention of atrial fibrillation, there was no apparent effect on the recurrence rate of the arrhythmia.[45,46] Paradoxically, digitalis's vagotonic activity and its shortening of the atrial refractory period may actually increase vulnerability to atrial fibrillation as well as its perpetuation. Similarly, the use of β- and calcium channel blockers, like digoxin, should be designated for rate control, not the normalization of rhythm. Notable exceptions to this rule occur when the use of these agents for rate control concurrently treats a primary abnormality that is precipitating atrial fibrillation, such as heart failure or high catecholamine states. For example, the success of β-blockers (but notably not digoxin or calcium channel blockers) in preventing atrial fibrillation in the aftermath of a coronary artery bypass operation is most likely mediated by catecholamine antagonism.[47,48]

Patients in whom adequate rate control cannot be achieved pharmacologically and in whom efforts to restore normal sinus rhythm have not been successful are candidates for ablative treatment of the AV node with implantation of a permanent ventricular pacemaker or catheter modification of the node. Radiofrequency energy employs unmodulated high-frequency AC current typically between 300 and 750 kHz to induce focal resistive heating at the point of application and thereby create discrete regions of tissue necrosis.[49] This technique has largely displaced high-energy DC current approaches to ablation.[50] When applied to the AV junction, radiofrequency catheter ablation is an irreversible means of creating complete heart block.[51,52] Although the ablative procedure is simple and safe, patients are left with lifelong pacemaker dependence. Moreover, the procedure does not result in AV synchrony or terminate atrial fibrillation and thus does not obviate the hemodynamic or thromboembolic consequences of the underlying rhythm disturbance, except for rate control. Radiofrequency catheter modification of the AV node, which selectively targets the "slow fibers" of the node, has been reported to result in rate control without the deliberate creation of pathologic AV block[53] and is proposed as an alternative to the complete ablation of AV node conduction. This technique, however, while not dependent on the deliberate creation of complete heart block, is limited by a 20% risk of inadvertent complete AV block, a relatively modest sustained reduction in the heart rate over time, and as-yet limited follow-up. Both AV node ablation and modification should, therefore, be regarded as a last resort for achieving rate control in patients who cannot tolerate drug therapy or for whom it is ineffective.

Surgical approaches to achieve rate control and restore the regularity of ventricular rhythm in atrial fibrillation have focused on isolating arrhythmia-prone regions of the atria. In the early and mid-1980s, two techniques, left atrial isolation and the corridor procedures, were pioneered. Left atrial isolation entailed an extensive atriotomy, essentially separating the left atrium from the right from an electrical standpoint.[54] This confined atrial fibrillation to the left atrium, resulting in sinus rate, but not sinus hemodynamics. In the corridor procedure, a strip of muscle lying between and containing the sinoatrial and AV nodes was surgically and electrically isolated from remaining atrial tissue.[55] This "corridor" allowed for the direct conduction of sinus node impulses to the AV node while surrounding atrial tissue continued to fibrillate. The corridor procedure resulted in the restoration of ventricular rate control by the sinus node and, like left atrial isolation, achieved the electrical but not mechanical equivalent of normal sinus rhythm. Because the left atrium (in the isolation operation) and the atria outside the confines of the corridor itself (in the corridor operation) continued to fibrillate, neither procedure obviated the hemodynamic nor thromboembolic risks from atrial fibrillation nor conferred any advantage over AV node ablation. Although left atrial isolation and corridor procedures are no longer done, these operations laid the foundation for newer techniques with greater promise for the complete cure of atrial fibrillation.

Finally, some patients with atrial fibrillation manifest a spontaneously controlled ventricular rate or wide extremes of fast and excessively slow rates, including prolonged sinus pauses at the termination of the arrhythmia. These manifestations of "brady-tachy" or sick sinus syndrome implicate a wider derangement in the conduction system than the presence of atrial fibrillation alone. Efforts to slow rapid ventricular rates in such patients often result in an exacerbation of bradycardia. Patients must frequently be managed with both drugs for slowing their tachycardia and a permanent pacemaker for protecting against extremes of bradycardia.[10]

Anticoagulation

Thromboembolism is a common and devastating complication of atrial fibrillation. It is estimated that

75% of thromboembolic events associated with atrial fibrillation involve the brain, 60% of which may result in death or permanent neurologic impairment.[56] The risk of thromboembolism in atrial fibrillation is linked to the associated disease process and, in patients undergoing cardioversion, to the duration of their arrhythmia. Patients with atrial fibrillation in the context of rheumatic mitral valve disease are an unusually high-risk group, 30% to 75% of whom have been reported to sustain one or more embolic complications during the course of their arrhythmia,[57-59] a risk that is 17 times higher than in age-, sex-, and blood pressure-matched controls.[60] Similarly, patients with long-standing atrial fibrillation undergoing elective cardioversion have a nearly sevenfold higher incidence of thromboembolism without than with chronic anticoagulation (5.3% versus 0.8%).[61] Chronic anticoagulation is mandated in such patients based on these historical data and retrospective studies.[62]

The optimal strategy for prophylaxis from thromboembolism is incompletely decided for the largest group of patients with either chronic or paroxysmal atrial fibrillation, in whom there is neither associated valvular heart disease nor planned cardioversion. Even after adjusting for other cardiovascular risk factors, the incidence of embolic complications in untreated patients with atrial fibrillation is threefold to fivefold that for those in normal sinus rhythm, or an absolute risk of about 5% per year,[63-65] and appears comparable for the arrhythmia in both its chronic and paroxysmal forms.[66,67] All told, nonvalvular atrial fibrillation probably accounts for more than 75,000 cases of stroke each year in the United States.

Independent clinical predictors of thromboembolic risk identified by compiled data from untreated patients participating in randomized treatment trials include a history of previous stroke or transient ischemic attack (relative risk, 2.5), diabetes mellitus (relative risk, 1.7), hypertension (relative risk, 1.6), and increasing age (relative risk, 1.4 per decade).[67] In addition, a recent incidence of heart failure (relative risk, 2.6) was found to predict thromboembolic events in the Stroke Prevention in Atrial Fibrillation (SPAF) trial. Echocardiographic evidence of moderate to severe left ventricular dysfunction and substantial left atrial enlargement also increased thromboembolic risk more than 2½ times.[68,69] In patients with atrial fibrillation not associated with any clinical risk factors (lone atrial fibrillation), age alone appears to add a modest incremental risk for thromboemboli: 0% in patients younger than 60 years, 1.6% annually in patients 60 to 69 years, and 2.1% annually in those 70 to 79 years of age.[65] The combination of age with clinical risk factors further compounds risk.

The choice of aspirin versus warfarin sodium as primary therapy in nonvalvular atrial fibrillation remains controversial. The results of numerous randomized trials that have addressed this question have been recently reviewed in this journal[70] and are summarized in Table 1.[71-77] Observations from these trials support the use of conservative treatment of atrial fibrillation with aspirin in young patients who are free of clinical risk factors associated with thromboembolic events.[78] When clinical risk factors are present, the administration of warfarin is the preferred treatment. In elderly patients (defined as those >75 years of age) with or without clinical risk factors, aspirin appears to be less effective than in younger patients whereas warfarin use is associated with a higher incidence of bleeding, including intracranial hemorrhage.[79] Whether lower-dose warfarin alone or in combination with aspirin may obviate this inordinately high bleeding risk without sacrificing antithrombotic efficacy is currently being studied.

Restoration of Normal Sinus Rhythm

Whether and how sinus rhythm should be restored and maintained pose the greatest controversies in, if not hazards of therapy for, atrial fibrillation. The resumption of normal sinus rhythm frequently translates into improved cardiac output, exercise tolerance, and well-being. In some patients with hypertrophic cardiomyopathy and other forms of severe diastolic dysfunction, restoring the atrial contribution to ventricular filling may alleviate symptoms of heart failure[73] and syncope[80] and may even be lifesaving.[81] Maintaining sinus rhythm also presumably lessens the risk of stroke so as to obviate the need for long-term anticoagulation. Thus, there are valid reasons for proceeding with plans for cardioversion with caution and in consideration of the questions: Can normal sinus rhythm be both restored and maintained? If so, how?

Nearly all patients with atrial fibrillation can be successfully cardioverted to normal sinus rhythm, at least transiently.[82] Whether sinus rhythm will persist after conversion, however, is the more challenging question and a far better criterion for judging whether to attempt cardioversion at all. Among the factors associated with the likelihood of restoring sinus rhythm, including age, sex, functional class, cardiomegaly, and left atrial and ventricular chamber size, only the previous duration of atrial fibrillation (<1 year)[83] and the absence of massive atrial enlargement (left atrial dimension <60 mm)[84] have predicted whether sinus rhythm will be maintained at one and six months following successful cardioversion. The "natural history" of reversion of an initially restored sinus rhythm to atrial fibrillation is disappointingly high, with less than one in four patients maintaining normal sinus rhythm after a year.[85] Whether to embark on a trial of cardioversion, therefore, requires an assessment of benefit (what the patient stands to gain by the restoration of sinus rhythm), procedural risk, and the likelihood of normal sinus rhythm being sustained.

It is uncertain if pharmacologic cardioversion offers any advantage over electrical cardioversion or if the efficacy of electrical cardioversion is necessarily augmented by the concomitant use of antiarrhythmic drugs. Recent transesophageal echocardiographic observations of spontaneous echo contrast and thrombus following electrical cardioversion have raised theoretical concerns over whether cardioversion itself is "prothrombotic" and

TABLE 1.—*Results of Randomized Trials of Warfarin Sodium and Aspirin for the Treatment of Atrial Fibrillation (AF)*

Study	*Trial Design*	*Treatment Assessment*	*Thromboembolic Events*	*Conclusions*
AFASAK (n = 1,007)*	All with chronic AF, 2-yr follow-up	Warfarin (INR, 2.8-4.2) versus aspirin, 75 mg/d, versus placebo	Reduced 58% by warfarin ($P < .03$)	Warfarin better than placebo and low-dose aspirin
SPAF I (n = 1,330)†	66% with chronic AF, 34% with paroxysmal AF, 1.3-yr follow-up	Aspirin, 325 mg/d, versus warfarin (INR, 2-3.5) versus placebo	Reduced 67% by warfarin ($P < .01$); 44% by aspirin ($P = .02$)	Warfarin and aspirin both reduced risk of emboli
SPAF II (n = 1,090)‡	Chronic and paroxysmal AF, 2-yr follow-up (patients >75 yr old), 3.1-yr follow-up (patients ≤75 yr old)	Warfarin (INR, 2-4.5) versus aspirin, 325 mg/d	No significant overall difference between aspirin and warfarin	Aspirin adequate in "low-risk" patients; warfarin associated with higher risk of bleeding
BAATAF (n = 420)§	Chronic and paroxysmal AF, 2.3-yr follow-up	Warfarin (INR, 1.5-2.7) versus placebo (aspirin use not controlled)	Reduced 86% by warfarin ($P < .002$)	Low-dose warfarin better than placebo
CAFA (n = 383)‖	Chronic and paroxysmal AF, 2.5-yr follow-up	Warfarin (INR, 2-3) versus placebo	Reduced 42% by warfarin (NS)	Trend favored warfarin use over placebo (prematurely stopped because of results from other trials)
SPINAF (n = 571)¶	Chronic AF, 1.7-yr follow-up	Warfarin (INR, 1.4-2.8) versus placebo	Reduced 79% by warfarin ($P < .002$)	Warfarin better than placebo
EAFT (n = 1,007)#	AF and recent TIA or stroke, 2.3-yr follow-up	Warfarin (INR, 2.5-4) versus aspirin, 300 mg/d, versus placebo	Reduced 69% by warfarin ($P = .04$), and 16% by aspirin (NS)	Patients with recent TIA or stroke are at substantial stroke risk, which is lessened by warfarin but not aspirin

INR = International Normalized Ratio, NS = not significant, TIA = transient ischemic attack

*From the Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK).[71]
†From the Stroke Prevention in Atrial Fibrillation trial I (SPAF I).[72]
‡From SPAF II.[73]
§From the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF).[74]
‖From the Canadian Atrial Fibrillation Anticoagulation (CAFA) trial.[75]
¶From the Stroke Prevention in Nonvalvular Atrial Fibrillation (VA Cooperative Study) (SPINAF) trial.[76]
#From the European Atrial Fibrillation Trial (EAFT).[77]

may enhance stroke risk because of atrial stunning from electrical energy.[86,87] No randomized trials, however, have yet compared either stroke risk or echocardiographic observations following electrical versus pharmacologic cardioversion. It has also been suggested that the delayed return of atrial mechanical function following cardioversion is more closely linked to the preceding duration of atrial fibrillation than to the method of cardioversion.[88] Thus, the duration of the arrhythmia rather than the means chosen to restore sinus rhythm may be the better predictor of increased thromboembolic risk accompanying cardioversion procedures.

The principal use of antiarrhythmic drugs appears to lie in the maintenance of sinus rhythm, once it has been restored by means of electrical or pharmacologic cardioversion (or both). The use of quinidine versus no antiarrhythmic therapy after the restoration of sinus rhythm in a meta-analysis of six such trials (808 patients) found a substantially higher proportion of treated patients remaining in normal sinus rhythm (Figure 1).[89] Other antiarrhythmic drugs may be effective in off-label use as alternatives to quinidine or in cases of quinidine-resistant arrhythmias.[90-94] Flecainide, the only alternative to quinidine approved by the Food and Drug Administration for the treatment of supraventricular tachycardia, should be reserved for use in patients without accompanying structural heart disease, particularly ischemic heart disease, in whom the risk of proarrhythmia may be enhanced.[95] Newer agents such as propafenone and sotalol have been found to be effective for atrial fibrillation refractory to conventional type IA agents even when associated with risk factors of left atrial enlargement, prolonged arrhythmia duration (>1 year), and previous drug failure, which would ordinarily predict against drug efficacy.[96] A successful maintenance of sinus rhythm at six months under these circumstances has been reported for 39% of patients treated with propafenone and 50% of those treated with sotalol. Amiodarone, possibly the most toxic of antiarrhythmic drugs, may be among the most effective for atrial fibrillation.[97,98] Although no prospective randomized trials comparing the safety and efficacy of amiodarone with conventional agents have yet been done, amiodarone's presumed lower proarrhythmia risk has gained it a favored status in the treatment of atrial fibrillation in patients with congestive cardiomyopathy. The long-term success of amiodarone in maintaining sinus rhythm, while greater than that of other agents, is far from universal: 60% at one year compared with 50% for quinidine and 34% for flecainide.[99] The short-term toxicity of amiodarone at low doses also appears comparable to these other agents. Unfortunately, even at low doses, the

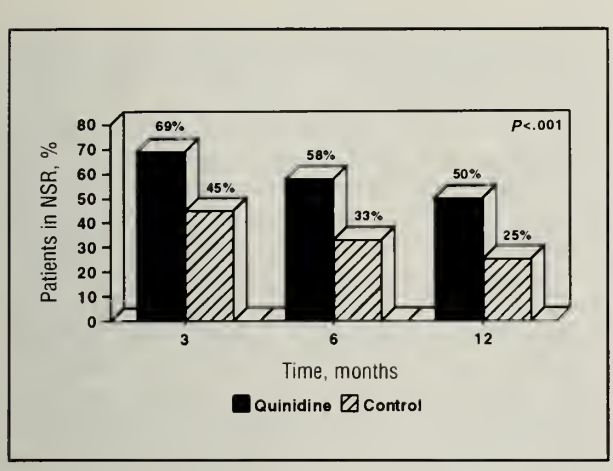

Figure 1.—The graphs show the proportion of patients remaining in normal sinus rhythm (NSR) after successful cardioversion followed by randomization to quinidine or no antiarrhythmic therapy (control group). The likelihood of sustained normal sinus rhythm was significantly greater in patients who were treated with quinidine (adapted by permission from Coplen et al[89]).

risk of long-term toxicity from the cumulative effects of amiodarone may only be delayed rather than eliminated.[100] Given these disappointing data, we might well ask whether any antiarrhythmic drug can do better than merely postponing the eventuality of chronic atrial fibrillation, and at what price.

Antiarrhythmic therapy comes at a price. For example, although treatment with quinidine is more likely to maintain normal sinus rhythm, such treatment is associated with a higher mortality and incidence of sudden or

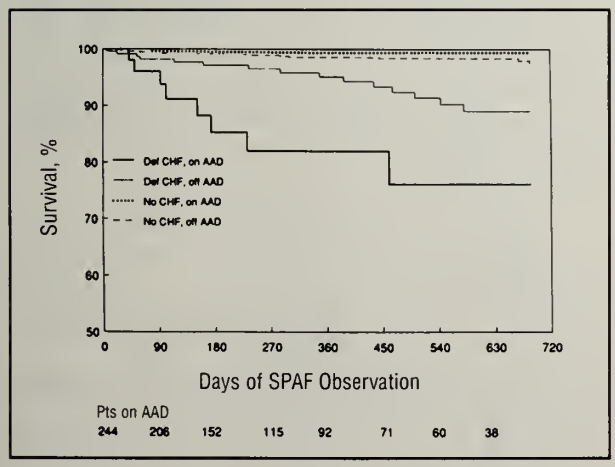

Figure 2.—Survival to cardiac-related death is shown in patients with atrial fibrillation. Survival curves are displayed for patients with and without a history of congestive heart failure (Def CHF and No CHF, respectively) and whether or not they were treated with antiarrhythmic medications for atrial fibrillation (on AAD and off AAD, respectively). Cardiac mortality was not altered by treatment with antiarrhythmic medications in patients with clinical heart failure. The frequency of cardiac-related death, however, was significantly higher in patients with heart failure who received antiarrhythmic medications ($P \leq .05$) (adapted by permission of the *Journal of the American College of Cardiology*[101]). SPAF = Stroke Prevention in Atrial Fibrillation

aborted sudden cardiac death.[84] A retrospective analysis of 244 patients who were treated with a variety of antiarrhythmic agents during the course of the SPAF anticoagulation trial corroborated concerns about the dangers of antiarrhythmic therapy. In the subgroup with congestive heart failure, treatment with antiarrhythmic agents substantially increased cardiac and arrhythmic mortality. After adjustment for other cardiac death predictors, including ventricular arrhythmias, the relative risk of cardiac-related death was 3.3 and of an arrhythmic death 5.8 in antiarrhythmic-drug recipients compared with nonrecipients. Moreover, these adverse effects on mortality were observed throughout the period of antiarrhythmic drug use and were not ascribable solely to the early consequences of therapy (Figure 2).[101]

Such sobering data demand a reappraisal of antiarrhythmic drug use in atrial fibrillation, especially in high-risk groups with substantial cardiac dysfunction. Ironically, these are the patients who stand to gain the most from sinus rhythm: those in whom heart failure symptoms and functional limitations might be considerably lessened with the restoration of atrioventricular synchrony. That there are risks and limitations to what can be accomplished with pharmacologic therapy in patients with atrial fibrillation does not preclude the use of drug treatment when necessary, but underscores the point that such treatment should not be routinely administered.

Recently, nonpharmacologic approaches entailing surgical or catheter ablation techniques and implantable devices have been proposed for the restoration of normal sinus rhythm in drug-refractory patients. Conceptually, the goal of ablative approaches is to interrupt all possible reentry circuits within the atria by reducing the critical mass necessary for their formation and perpetuation. Unlike earlier corridor and atrial isolation surgical procedures, whose intent was merely to control the ventricular rate, the anticipated result of newer approaches is the abolition of atrial fibrillation itself. In the Maze procedure, the atria are surgically divided into different compartments by several incisions so that no impulse is able to traverse a path of sufficient length to support a reentry circuit before encountering and being diverted by a nonconducting suture line. In addition, these incisions are positioned so as to allow for the conduction of a sinoatrial impulse throughout the atrium to the AV node, thus preserving electromechanical function (Figure 3).[102] Although performed to date in only a small number of patients and with limited follow-up, the Maze operation has been successful in curing atrial fibrillation while preserving both electrical and mechanical atrial activity in 99% of patients (by surgical therapy alone in 90% and by surgical therapy plus antiarrhythmic medications in 9%), with an operative mortality of 1.3%.[54,103] Attempts to duplicate the surgical Maze procedure or to undertake other innovative ablative approaches to atrial fibrillation using transvenous radiofrequency catheter techniques are still in their infancy[104-106] but offer promise for future cure without the need for surgical intervention. Atrial defibrillators, analogous to implantable

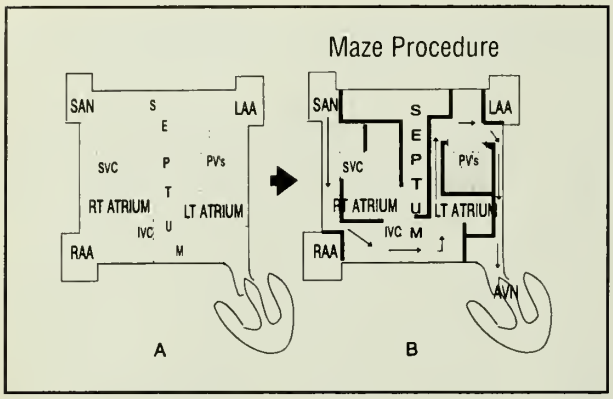

Figure 3.—The conceptual schematic diagram shows normal atrial anatomy (A) and depicts the Maze procedure for atrial fibrillation (B). In the Maze procedure, both atrial appendages are excised and the pulmonary veins (PVs) are isolated. Appropriately placed atrial incisions not only interrupt the conduction routes of the most common reentrant circuits, but also direct the sinus impulse from the sinoatrial node (SAN) to the atrioventricular node (AVN) along a specified route (arrows). The entire atrial myocardium (except for the atrial appendages and the PVs) is electrically activated. This is accomplished by providing for multiple blind alleys off the main conduction route between the SAN and AVN, thereby preserving atrial mechanical function. IVC = inferior vena cava, LAA = left atrial appendage, LT = left, RAA = right atrial appendage, RT = right, SVC= superior vena cava (adapted by permission of the *Journal of Thoracic and Cardiovascular Surgery*[102]).

devices used to treat malignant ventricular arrhythmias, are also in development,[107] although many questions remain to be addressed about their safety and reliability. Thus, at present, although techniques appear promising, a definitive cure for atrial fibrillation remains elusive.

Recurrences

The natural history of atrial fibrillation is characterized by repeated recurrences. It is not always clear at what point and in which patients further efforts to maintain sinus rhythm are futile. Available data suggest that the likelihood of maintaining normal sinus rhythm for at least six months declines with each successive cardioversion.[108] For some patients, this may justify conceding efforts to maintain sinus rhythm after three or four attempts at cardioversion because in only 25% of such patients is sinus rhythm likely to be restored more than transiently. Alternatively, if recurrences of atrial fibrillation are viewed as "events" and not as a therapeutic failure, for patients to derive six or more months of benefit from each successive cardioversion could also be seen as a reasonable therapeutic goal in those with life-limiting symptoms. Thus, patients are likely to have several recurrences of their arrhythmia over their course of treatment, and the risk of recurrence should not necessarily deter efforts to restore sinus rhythm.

Future Directions

Several ongoing and planned clinical trials are addressing the many remaining controversies and uncertainties in the management of atrial fibrillation. A third SPAF trial (SPAF III), a second Atrial Fibrillation, Aspirin, Anticoagulation Study of Copenhagen (AFASAK II), and an ongoing Dutch trial (PATAF) are investigating new antithrombotic regimens, including "minidose" warfarin for stroke prophylaxis.[78] The AFFIRM trial will soon be randomly assigning patients in a multicenter prospective trial evaluating antiarrhythmic strategies (the restoration of normal sinus rhythm versus rate control) in atrial fibrillation, including a cost analysis of these options (H. Leon Greene, MD, oral communication, January 1996). Finally, new diagnostic and therapeutic technologies involving transesophageal echocardiography, catheter ablation, and implantable devices may one day change our entire approach to this timeless problem.[109]

Summary

The approach to and treatment of patients with atrial fibrillation must be tailored for each patient. As "bare essentials," issues of rate control and anticoagulation need to be addressed in all patients because these contribute substantially to morbidity. The restoration of sinus rhythm should be approached early in the course of atrial fibrillation because success appears related to the duration of the arrhythmia, and early treatment may even prevent the progression of atrial disease. Restoring sinus rhythm should also be approached cautiously, particularly among asymptomatic patients with atrial fibrillation, who (being already asymptomatic) have little to gain in terms of improved well-being and possibly much to lose from the toxic or even lethal effects of antiarrhythmic agents. A cure for this long-time affliction remains elusive. For the foreseeable future, management will need to rest on a thorough evaluation for an underlying cause, controlling extremes of rate, protecting against thromboembolic complications, and continuing to agonize over whether and how sinus rhythm should be restored.

REFERENCES

1. Halperin JL, Hart RG: Atrial fibrillation and stroke: New ideas, persisting dilemmas. Stroke 1988; 19:937-941

2. Copenhagen City Heart Study. Scand J Soc Med 1989; 17(suppl):124-125

3. Carins JA, Connolly SJ: Nonrheumatic atrial fibrillation: Risk of stroke and role of antithrombotic therapy. Circulation 1991; 84:469-480

4. Godtfredsen J: Atrial fibrillation: Course and prognosis—A follow-up study of 1212 cases, *In* Kulbertus HE, Olsson SB, Schlepper M (Eds): Atrial Fibrillation. Mölndal, Sweden, AB Hassle, 1982, pp 134-145

5. Robles de Medina EO, Bernard R, Coumel P, Damato AN, Fisch C: WHO/ISFC Task Force: Definitions of terms related to cardiac rhythm. Am Heart J 1978; 95:796-806

6. Waldo AL: Basic mechanisms of atrial fibrillation and flutter. Cardiol Rev 1993; 1:16-23

7. Meijler FL: Atrial fibrillation: A new look at an old arrhythmia. J Am Coll Cardiol 1983; 2:391-393

8. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. Circulation 1995; 92:1954-1968

9. Petersen P, Kastrup J, Brinch K, Godtfredsen J, Boysen G: Relation between left atrial dimension and duration of atrial fibrillation. Am J Cardiol 1987; 60:382-384

10. Sgarbossa EB, Pinski SL, Maloney JD, et al: Chronic atrial fibrillation and stroke in paced patients with sick sinus syndrome—Relevance of clinical characteristics and pacing modalities. Circulation 1993; 88:1045-1053

11. Naito M, David D, Michelson EL: The hemodynamic consequences of cardiac arrhythmias—Evaluation of the relative roles of abnormal atrioventricular sequencing, irregularity of ventricular rhythm and atrial fibrillation in a canine model. Am Heart J 1983; 106:284-291

12. Khaja F, Parker JO: Hemodynamic effects of cardioversion in chronic atrial fibrillation. Arch Intern Med 1972; 129:433-440

13. Kannel WB, Abbott RD, Savage DD, McNamara PM: Epidemiologic features of chronic atrial fibrillation: The Framingham study. N Engl J Med 1982; 306:1018-1022

14. Friedman HZ, Weber-Bornstein N, Deboe SF, Mancini GB: Cardiac care unit admission criteria for suspected acute myocardial infarction in new onset atrial fibrillation. Am J Cardiol 1987; 59:866-869

15. Lauer MS, Eagle KA, Buckley JM, DeSanctis RW: Atrial fibrillation following coronary artery bypass surgery. Prog Cardiovasc Dis 1989; 31:367-378

16. Sawin CT, Geller A, Wolf PA, et al: Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994; 331:1249-1252

17. Coumel P, Leclerq J: Cardiac arrhythmias and the autonomic nervous system, *In* Levy M, Scheinman M (Eds): Cardiac Arrhythmias—From Diagnosis to Therapy. Mt Kisco, NY, Futura, 1984, pp 37-55

18. Coumel P, Friocourt P, Mugica J, Attuel P, Leclercq JF: Long-term prevention of vagal atrial arrhythmias by atrial pacing at 90/minute: Experience with 6 cases. PACE 1983; 6(pt 1):552-560

19. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA: Independent risk factors for atrial fibrillation in a population-based cohort: The Framingham Heart Study. JAMA 1994; 271:840-844

20. Kopecky SL, Bersh BJ, McGoon MD, et al: The natural history of lone atrial fibrillation: A population-based study over three decades. N Engl J Med 1987; 317:669-674

21. Evans W, Swann P: Lone atrial fibrillation. Br Heart J 1954; 6:189-194

22. Roark SF, McCarthy EA, Lee KL, Pritchett EL: Observations on the occurrence of atrial fibrillation in paroxysmal supraventricular tachycardia. Am J Cardiol 1986; 57:571-575

23. Sung RJ, Castellanos A, Mallon SM, Bloom MG, Gelband H, Myerburg RJ: Mechanisms of spontaneous alternation between reciprocating tachycardia and atrial flutter-fibrillation in the Wolff-Parkinson-White syndrome. Circulation 1977; 56:409-416

24. Sharma AD, Klein GJ, Guiraudon GM, Milstein S: Atrial fibrillation in patients with Wolff-Parkinson-White syndrome: Incidence after surgical ablation of the accessory pathway. Circulation 1985; 72:161-169

25. Haissaguerre M, Fisher B, Labbé T, et al: Frequency of recurrent atrial fibrillation after catheter ablation of overt accessory pathways. Am J Cardiol 1992; 69:493-497

26. Meijler FL: An 'account' of digitalis and atrial fibrillation. J Am Coll Cardiol 1985; 5:60A-68A

27. Kim YI, Noble RJ, Zipes DP: Dissociation of the inotropic effect of digitalis from its effect on atrioventricular conduction. Am J Cardiol 1975; 36: 459-467

28. Gaffney RE, Kahn JB, Van Maanen EF, et al: A mechanism of the vagal effect of cardiac glycosides. J Pharmacol Exp Ther 1958; 122:423-429

29. Watanabe AM: Digitalis and the autonomic nervous system. J Am Coll Cardiol 1985; 5:35A-42A

30. Mendez R, Mendez C: The action of cardiac glycosides on the refractory period of heart tissues. J Pharmacol Exp Ther 1953: 107:24-26

31. Moe GK, Abildskov JA: Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. Circ Res 1964; 14:447-460

32. Sorstein L: Role of digitalis in ventricular rate control in atrial fibrillation, *In* Kulbertus HE, Ollson SB, Schlepper M (Eds): Atrial Fibrillation. Mölndal, Sweden, AB Hassle, 1982, pp 284-292

33. Campbell RWF, Smith RA, Gallagher JJ, et al: Atrial fibrillation in the pre-excitation syndrome. Am J Cardiol 1977; 40:514-520

34. Sellers TD Jr, Bashore TM, Gallagher JJ: Digitalis in the pre-excitation syndrome—Analysis during atrial fibrillation. Circulation 1977; 56:260-267

35. Garratt C, Antoniou A, Ward D, Camm AJ: Misuse of verapamil in pre-excited atrial fibrillation. Lancet 1989; 1:367-369

36. Morady F, DiCarlo LA Jr, Baerman JM, De Buitleir M: Effect of propranolol on ventricular rate during atrial fibrillation in the Wolff-Parkinson-White syndrome. PACE 1987; 10(pt 1):492-496

37. Falk RH: Control of the ventricular rate in atrial fibrillation, *In* Falk RH, Podrid PJ (Eds): Atrial Fibrillation: Mechanisms and Management. New York, NY, Raven Press, 1992, pp 255-282

38. Peters KG, Kienzle MG: Severe cardiomyopathy due to chronic rapidly conducted atrial fibrillation: Complete recovery after restoration of sinus rhythm. Am J Med 1988; 85:242-244

39. Rodriguez LM, Smeets JL, Xie B, et al: Improvement in left ventricular function by ablation of atrioventricular nodal conduction in selected patients with lone atrial fibrillation. Am J Cardiol 1993; 72:1137-1141

40. Twidale N, Sutton K, Bartlett L, et al: Effects on cardiac performance of atrioventricular node catheter ablation using radiofrequency current for drug-refractory atrial arrhythmias. PACE Pacing Clinic Electrophysiol 1993; 16: 1275-1284

41. Grogan M, Smith HC, Gersh BJ, Wood DL: Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol 1992; 59:1570-1573

42. Roth A, Harrison E, Mitani G, Cohen JJ, Rahimtoola SH, Elkayam U: Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. Circulation 1986; 73:316-324

43. Rawles JM: What is meant by a 'controlled' ventricular rate in atrial fibrillation? Br Heart J 1990; 63:157-161

44. Falk RH, Knowlton AA, Bernard SA, Gotlieb NE, Battinelli NJ: Digoxin for converting recent-onset atrial fibrillation to sinus rhythm: A randomized, double-blinded trial. Ann Intern Med 1987; 106:503-506

45. Rawles JM, Metcalf MF, Jennings K: Time of occurrence, duration and ventricular rate of paroxysmal atrial fibrillation: The effect of digoxin. Br Heart J 1990; 63:225-227

46. Anderson JL, Gilbert EM, Albert BG, Flecainide Supraventricular Tachycardia Study Group: Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: A multicenter double-blind, crossover study of flecainide and placebo with transtelephonic monitoring. Circulation 1989; 89:1557-1570

47. Kowey PR, Taylor JE, Rials S, Marinchak RA: Meta-analysis of the effectiveness of prophylactic drug therapy in preventing supraventricular arrhythmia early after coronary artery bypass grafting. Am J Cardiol 1992; 69:963-965

48. Andrew TC, Reimold SC, Berlin JA, et al: Prevention of supraventricular arrhythmia after coronary artery bypass surgery: A meta-analysis of randomized control trials. Circulation 1990; 84 (suppl III):236-244

49. Jazayeri MR, Deshpande S, Dhala A, Blanck Z, Sra J, Akhtar M: Transcatheter mapping and radiofrequency ablation of cardiac arrhythmias, *In* O'Rourke RA (Ed): Current Problems in Cardiology, Vol 19. St Louis, Mo, Mosby, 1994, pp 285-396

50. Morady F, Calkins H, Langberg JJ, et al: A prospective randomized comparison of direct current and radiofrequency ablation of the atrioventricular junction. J Am Coll Cardiol 1993; 21:102-109

51. Huang SK, Bharati S, Graham AR, Lev M, Marcus FI, Odell RC: Closed chest catheter dissection of the atrioventricular junction using radiofrequency energy: A new method of catheter ablation. J Am Coll Cardiol 1987; 9:349-358

52. Sousa J, el-Atassi R, Rosenheck S, Calkins H, Langberg J, Morady F: Radiofrequency catheter ablation of the atrioventricular junction from the left ventricle. Circulation 1991; 84:567-571

53. Williamson BD, Man KC, Daoud E, Niebauer M, Strickberger SA, Morady F: Radiofrequency catheter modification of atrioventricular conduction to control the ventricular rate during atrial fibrillation. N Engl J Med 1994; 331:910-917

54. Cox JL, Boineau JP, Schuessler RB, et al: Electrophysiologic basis, surgical development, and clinical results of the Maze procedure for atrial flutter and atrial fibrillation. Adv Cardiac Surg 1995; 6:1-67

55. Defauw JJ, Guiraudon GM, van Hemel NM, Vermeulen FEE, Kingma JH, de Bakker JMT: Surgical therapy of paroxysmal atrial fibrillation with the 'corridor' operation. Ann Thorac Surg 1992; 53:564-571

56. Fisher CM: Embolism in atrial fibrillation, *In* Kulbertus HE, Olsson SB, Schlepper M (Eds): Atrial Fibrillation. Mölndal, Sweden, AB Hassle, 1982, pp 192-210

57. Sherman DG, Hart RG, Easton JD: The secondary prevention of stroke with atrial fibrillation. Arch Neurol 1986; 43:68-70

58. Starkey I, Warlow C: The secondary prevention of stroke in patients with atrial fibrillation. Arch Neurol 1986; 43:66-68

59. Siegel R, Tresch DD, Keelan MH Jr, Brooks HL: Effects of anticoagulation on recurrent systemic emboli in mitral stenosis. Am J Cardiol 1987; 60:1191-1192

60. Wolf PA, Dawber TR, Thomas HE, Kannel WB: Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. Neurology 1978; 28:973-977

61. Bjerkelung CJ, Oring OM: The efficacy of anticoagulant therapy in preventing embolism related to DC electrical conversion of atrial fibrillation. Am J Cardiol 1969; 23:208-216

62. Hirsh J, Fuster V: Guide to anticoagulant therapy part 2: Oral anticoagulants. Circulation 1994; 89:1469-1480

63. Flegel KM, Hanley J: Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. Stroke 1989; 20:1000-1004

64. Onundarson PT, Thorgeirsson G, Jonmundsson E, Sigfusson N, Hardarson T: Chronic atrial fibrillation—Epidemiologic features and 14 year follow-up: A case control study. Eur Heart J 1987; 8:521-527

65. Wolf PA, Kannel WB, McGee DL, Meeks SL, Bharucha NE, McNamara PM: Duration of atrial fibrillation and imminence of stroke: The Framingham study. Stroke 1984; 14:664-667

66. Albers GW: Atrial fibrillation and stroke: Three new studies, three remaining questions. Arch Intern Med 1994; 154:1443-1448

67. Atrial Fibrillation Investigators: Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Arch Intern Med 1994; 154: 1449-1457

68. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation—I. Clinical features of patients at risk. Ann Intern Med 1992; 116:1-5

69. Stroke Prevention in Atrial Fibrillation Investigators: Predictors of thromboembolism in atrial fibrillation—II. Echocardiographic features of patients at risk. Ann Intern Med 1992; 116:6-12

70. Wipf JE: Anticoagulation and atrial fibrillation—Putting the results of clinical trials into practice. West J Med 1995; 163:145-152

71. Peterson P, Boysen G, Godtfredsen J, Anderson E, Andersen B: Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK study. Lancet 1989; 1:175-178

72. Stroke Prevention in Atrial Fibrillation Investigators: Stroke prevention in atrial fibrillation study: Final results. Circulation 1991; 84:527-539

73. Samukawa M, Hasegawa K, Harada Y, et al: Clinical features and significance of hypertrophic cardiomyopathy with atrial fibrillation. J Cardiol 1987; 17:465-474

74. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators: The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990; 323:1505-1511

75. Connolly SJ, Laupacis A, Gent M, Roberts MS, Cairns JA, Joyner C: Canadian Atrial Fibrillation Anticoagulation (CAFA) study. J Am Coll Cardiol 1991; 18:349-355

76. Ezekowitz MD, Bridgers SL, James KE, et al, for the Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators: Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. N Engl J Med 1992; 327:1406-1412

77. European Atrial Fibrillation Trial Study Group: Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342:1255-1262

78. Major ongoing stroke trials. Stroke 1994; 25:541-545

79. Stroke Prevention in Atrial Fibrillation Investigators: Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study. Lancet 1994; 343:687-691

80. Brembilla-Perrot B, Terrier de La Chaise A, Beurrier D: [Paroxysmal atrial fibrillation: Main cause of syncope in hypertrophic cardiomyopathy.] Arch Mal Coeur Vaiss 1993; 86:1573-1578

81. Madariaga I, Carmona JR, Mateas FR, Lezaun R, de los Archos E: Supraventricular arrhythmia as the cause of sudden death in hypertrophic cardiomyopathy. Eur Heart J 1994; 15:134-137

82. Lown B: Electrical reversion of cardiac arrhythmias. Br Heart J 1967; 29:469-489

83. Dittrich HC, Erickson JS, Schneiderman T, Blacky AB, Savides T, Nicod PH: Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. Am J Cardiol 1989; 63:193-197

84. Brodsky MA, Allen BJ, Capparelli EV, Luckett CR, Morton R, Henry WL: Factors determining maintenance of sinus rhythm after chronic atrial fibrillation with left atrial dilatation. Am J Cardiol 1989; 63:1065-1068

85. Suttorp MJ, Kingma JH, Koomen EM, van't Hof A, Tijssen JGP, Lie KI: Recurrence of paroxysmal atrial fibrillation or flutter after successful cardioversion in patients with normal left ventricular function. Am J Cardiol 1993; 71:710-713

86. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP: Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: Evidence for 'atrial stunning' as a mechanism of thromboembolic complications. J Am Coll Cardiol 1994; 23:307-316

87. Grimm RA, Steward WJ, Maloney JD, et al: Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: Characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993; 22:1359-1366

88. Manning WJ, Silverman DI, Katz SE, et al: Impaired left atrial mechanical function after cardioversion: Relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994; 23:1535-1540

89. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC: Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: A meta-analysis of randomized controlled trials. Circulation 1990; 82: 1106-1116

90. Szekely P, Sideris DA, Batson GA: Maintenance of sinus rhythm after atrial fibrillation. Br Heart J 1970; 32:741-746

91. Karlson BW, Torstensson I, Abjörn C, Jansson SO, Peterson LE: Disopyramide in the maintenance of sinus rhythm after electroconversion of atrial fibrillation—A placebo-controlled one-year follow-up study. Eur Heart J 1988; 9:284-290

92. Antman EM, Beamer AD, Cantillon C, McGowan N, Goldman L, Friedman PL: Long-term oral propafenone therapy for suppression of refractory symptomatic atrial fibrillation and atrial flutter. J Am Coll Cardiol 1988; 12:1005-1011

93. Jull-Moller S, Edvardsson N, Rehnqvist-Ahlberg N: Sotalol versus quinidine for maintenance of sinus rhythm after direct current conversion of atrial fibrillation. Circulation 1990; 82:1932-1934

94. Gosselink AT, Crijns HJ, Van Gelder IC, Hillige H, Wiesfeld AC, Lie KI: Low-dose amiodarone for maintenance of sinus rhythm after cardioversion of atrial fibrillation or flutter. JAMA 1991; 267:3289-3293

95. Berns E, Rinkenberger RL, Jeang MK, Dougherty AH, Jenkins M, Naccarelli GV: Efficacy and safety of flecainide acetate for atrial tachycardia or fibrillation. Am J Cardiol 1987; 59:1337-1341

96. Antman EM, Beamer AD, Cautillon C, McGowan N, Friedman PL: Therapy of refractory symptomatic atrial fibrillation and atrial flutter: A staged care approach with new antiarrhythmic drugs. J Am Coll Cardiol 1990; 15: 698-707

97. Wilson JS, Podrid PJ: Side effects from amiodarone. Am Heart J 1991; 121:158-171

98. Disch DL, Greenberg ML, Holzberger PT, Malenka DJ, Birkmeyer JD: Managing chronic atrial fibrillation: A Markov decision analysis comparing warfarin, quinidine and low-dose amiodarone. Ann Intern Med 1994; 120:449-457

99. Zarembski DG, Nolan PE, Slack MK, Caruso AC: Treatment of resistant atrial fibrillation: A meta-analysis comparing amiodarone and flecainide. Arch Intern Med 1995; 155:1885-1891

100. CASCADE Investigators: Randomized antiarrhythmic drug therapy in survivors of cardiac arrest: The CASCADE study. Am J Cardiol 1993; 72: 280-287

101. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG: Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. J Am Coll Cardiol 1992; 20:527-532

102. Cox JL, Schuessler RB, D'Agostino HJ, et al: The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991; 101:569-583

103. Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG: Five-year experience with the Maze procedure for atrial fibrillation. Ann Thorac Surg 1993; 56:814-823

104. Swartz JF, Pellersels G, Silvers J, Patten L, Cervantez D: A catheter-based curative approach to atrial fibrillation in humans. Circulation 1994; 90(suppl II):I-335

105. Haissaguerre M, Gencel L, Fisher B, et al: Successful catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 1994; 5:1045-1052

106. Haissaguerre M, Marcus FI, Fisher B, Clémenty J: Radiofrequency catheter ablation in unusual mechanisms of atrial fibrillation: Report of three cases. J Cardiovasc Electrophysiol 1994; 5:743-751

107. Mugatrod FD, Slade AKB, Sopher SM, Rowland E, Ward DE, Camm AJ: Efficacy and tolerability of transvenous low energy cardioversion of paroxysmal atrial fibrillation in humans. J Am Coll Cardiol 1995; 25:1347-1353

108. Thibault B, Talajic M, Dubuc M, Roy D: Electrical cardioversion for atrial fibrillation: How many attempts are sufficient? (Abstr) Circulation 1993; 88(suppl II):340

109. Manning WJ, Sileman DI, Keighley CS, Oettgen P, Douglas PS: Transesophageal echocardiographically facilitated early cardioversion from atrial fibrillation using short-term anticoagulation: Final results of a prospective 4.5-year study. J Am Coll Cardiol 1995; 25:1354-1361

Female Urethral Syndrome
A Female Prostatitis?

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The cause of the female urethral syndrome has previously been obscure, as it has been associated by definition with a lack of objective findings but a plethora of subjective complaints of retropubic pressure, dyspareunia, urinary frequency, and dysuria. There is now strong evidence that the microscopic paraurethral glands connected to the distal third of the urethra in the prevaginal space are homologous to the prostate. They stain histologically for prostate-specific antigen and, like the prostate, are subject to both infection and cancer. The most important aspect of recognizing this microscopic "female prostate" as an anatomic feature is that its infections may completely explain many cases of the urethral syndrome. Further, the diagnosis is not elusive if trained clinicians palpate for localized and objective paraurethral tenderness through the anterior vagina wall to one or both sides of the urethra. Treatment parallel to that for male prostatitis is usually rewarded by the elimination of symptoms and the objective finding of the loss of tenderness of the paraurethral glands. As with prostatitis, the localized problem often recurs. It is time to alert primary care physicians to this disorder and to eliminate the widespread practice of treating affected women with either invasive urethral dilation or tranquilizers.

(Gittes RF, Nakamura RM: Female urethral syndrome—A female prostatitis? West J Med 1996; 164:435-438)

For 30 years, the urethral syndrome has been a catchall diagnosis for the frequently seen women who have symptoms resembling a lower urinary tract infection but whose objective findings are negative—that is, no abnormal midstream urinalysis findings, no positive bacterial culture, and no obvious finding on a pelvic examination.[1,2] Similar symptoms in a man would suggest prostatitis and would lead to microscopic examination of the prostatic secretions for the presence of inflammatory cells.[3] Is there a "female prostate" to also investigate?

'Female Prostate'

For many years, anatomists have described homologues of the prostate in the little glands adjacent to the female urethra. These were first described by Regeneri de Graaf in 1672.[4] In 1880 Skene described the two main ducts that bear his name and that drain the most distal of the glands to their openings, which are adjacent to the meatus of the female urethra.[5] These were anatomical curiosities until the late 1940s and 1950s, when Huffman made careful serial sections and reconstructions to describe the female paraurethral glands branching out from the urethral lumen into the adjacent soft tissue alongside the distal two thirds of the urethra (Figure 1).[6,7] He noted columnar epithelium that stained with mucicarmine. He wrote that, in postmortem tissues, "inflammatory reactions in and about the ducts and glands are common."[6(p97)]

In a scholarly dissertation, Huffman related that paraurethral ducts and glands play an important role in nonspecific urethritis, including the occasional abscess or cysts that may develop into a female urethral diverticulum. He also described adenomas and rare adenocarcinomas arising from these glands.

Long before Huffman's work, the role of the paraurethral glands had been discounted. Cabot and Shoemaker dismissed the glands themselves as simply invaginations of the urethral mucosa and suggested that glands of the female urethra, except Skene's glands, do not play an important role in infections of the female urinary tract.[8] The work of Huffman, reported in the gynecologic literature, did not affect the practice of urologists who were by then converted to an obstructive interpretation of female urethral problems and practiced aggressive urethral dilatations and surgical urethrotomies for recurrent urethral symptoms.[9-11] A lone exception among urologists was one who advocated visualization of the openings of the paraurethral ducts and with a tiny probe slicing them open with electrocautery into the urethral lumen, with anecdotal uniform "success."[12]

In the past decade, the availability of the specific histochemical staining for prostate-specific antigen (PSA) has rehabilitated the status of the paraurethral glands and

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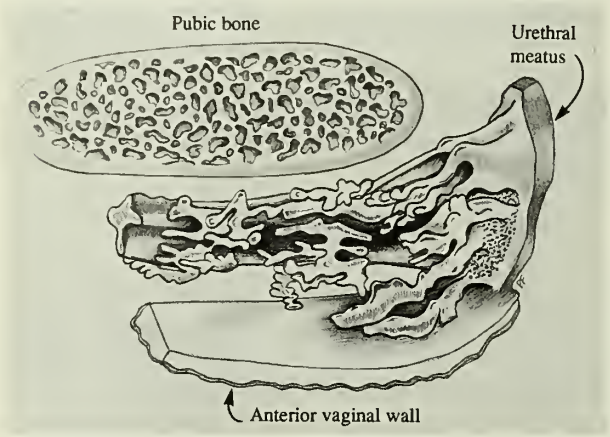

Figure 1.—A 3-dimensional reconstruction from histologic serial sections of normal female urethra is shown. The paraurethral ducts and glands are invariably found alongside the distal two thirds of the urethra (from Huffman[6]).

spotlighted them as the homologue of the prostate.[13-15] Earlier research on the small rodent *Mastomys natalensis* had been reported in which a well-defined "prostatic gland" was described in all of the female animals.[16] These rodents have been recently used as an animal model for chronic bacterial prostatitis in both male and female animals with *Escherichia coli*.[17]

The rare clinical adenocarcinomas of the distal female urethra are now recognized as primary tumors of the "female prostate" due to their specific staining with PSA and prostate-specific acid phosphatase.[18-20]

Urethral Syndrome

The term "urethral syndrome" has been used for nearly 30 years to describe a condition that occurs in a large number of women who present with symptoms of retropubic pressure, urinary frequency, and dysuria, often with dyspareunia, but who on examination do not have either vaginal infection or cystitis as determined by cultures and colony counts of midstream urine specimens.[1] Urologic textbooks have had to deal with this disorder for years because it is recognized that the patients who are so labeled form a large part of the outpatient practice of general physicians and gynecologists and even more so of urologists who are referred untreated or unresolved chronic cases.[2] In one gynecologic review, it was estimated that more than 5 million office visits per year were for this problem.[21] An astounding variety of treatments have been practiced over the years, covering the full spectrum from aggressive surgical excision of the periurethral tissue,[10] internal urethral cutting procedures, and forceful overdilations of the urethra[9,11,12] to the use of anxiolytic and tricyclic antidepressant drugs ("tranquilizers" [diazepam, amitriptyline]) as the sole treatment. This last therapy has been based on the idea that the women had functional complaints with pelvic floor muscle spasm.[22,23] In the only prospective study of treatment alternatives, short courses of the urinary antibiotics nitrofurantoin and the combination of trimethoprim and sulfamethoxazole were included, as well as anticholinergic agents and urethral dilations, with no treatment controls.[24] Although all treatments were judged ineffective and it was suggested that treatment be supportive and "harmless," aggressive management continues to be widely practiced today.

In a chapter dealing with this syndrome in a textbook of urology, Messing stressed that the diagnosis was one of excluding other disorders that have objective findings.[2] He further commented that "pelvic examination (with the possible exception of mild anterior distal vaginal tenderness) . . . must reveal no abnormalities that could explain the symptoms."[2(p1087)] The textbook answer to the cause of the urethral syndrome has continued to be uncertain, with a menu of obstructive, infectious, neurogenic, and psychogenic possibilities being offered.[2(p1087)] The role of the infection that has been repeatedly investigated was challenged by the lack of polymorphonuclear leukocytes in the urine and the low bacterial colony counts in contrast to the findings associated with overt cystitis. Experts in urinary infection attempted to define offending organisms and recognized that antibiotic therapy was empirically effective.[25,26] *Chlamydia* species were found in the urethra of young women.[25] Even the possibility of fastidious organisms has been indicated.[27] But none of the recent investigators have correlated the diagnosis of the infection to the anatomically cryptic paraurethral glands.

The possible psychogenic cause that has been used as the basis for treatment with anxiolytic drugs for the past 20 years has been supported by various publications studying the response of such patients to personality tests (Minnesota Multiphasic Personality Inventory),[28] measurements of pelvic floor tension,[22] or external sphincter reactivity.[23] A recent psychological study sagely suggests that perhaps these were normal women responding to the stress of continuing symptoms and inadequate diagnosis and treatment.[29]

The advanced imaging technology with internal vaginal ultrasonography was applied to patients with the urethral syndrome by a Japanese group.[30] This group reported no imaging differences from those of controls, but rather the simple finding that "tenderness at the upper frontal wall of the vagina was seen in 10 of 11 patients with urethral syndrome . . . and in 1 of 9 with a normal bladder."[30(p1094)] They concluded that "internal examination for tenderness at the frontal wall of the vagina" was "useful for diagnosis and follow-up of the patients with urethral syndrome."[30(p1094)] No correlation of this tenderness with the paraurethral glands was recognized.

Diagnosis by Pelvic Examination

Rather than using a diagnosis of exclusion, as in the past, we have relied on a careful pinpoint palpation of the soft tissue of the anterior vaginal wall on each side of the urethra to make a clinical diagnosis of infection of the paraurethral glands in cases that would otherwise fall into the category of urethral syndrome. As shown in Figure 2, digital examination of the small volume of tissue involved by this symptomatic inflammation permits a strong presumptive diagnosis of infection of the paraurethral

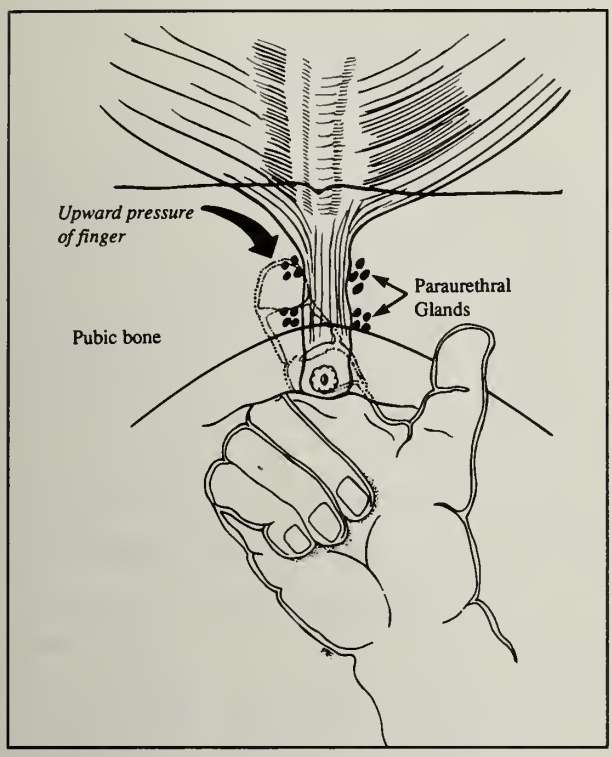

Figure 2.—Upward fingertip pressure against the pubic bone lateral to the urethra elicits localized tenderness when the paraurethral glands are infected.

glands. The examination certainly parallels a digital rectal examination that finds localized prostate gland tenderness that is then treated with antibiotics as a prostatitis. Of course, fluid is not available for expression by massage and microscopic analysis, so treatment becomes empirical on the basis of these localized findings. More invasive diagnostic maneuvers do not appear justified.

Treatment of Female Prostatitis

The treatment of the detected tenderness of the paraurethral glands is based on the same premises that clinicians use in the treatment of men with prostatic infections. First, the paraurethral glands and any organisms within them are isolated from therapeutic concentrations of antibiotics in the urine, requiring tissue-penetrating agents. Second, the relative inaccessibility and presumed stagnation of the glands may require long-term treatment with tissue-penetrating antibiotics to achieve a cure.

Because of the findings of investigators characterizing the small number of organisms that reach the urethral lumen,[25] younger women are treated with tetracycline or erythromycin on the presumption that they have *Chlamydia* species in those glands. They are treated for two to four weeks. Older women or younger women for whom the first treatment fails are given a quinolone for at least a month.[31] Hot sitz baths are also advised and seem to help during the acute phase (as in male prostatitis).

Antibiotic treatment usually eliminates the symptoms. An objective vaginal reexamination in follow-up usually confirms the decrease or absence of tenderness in the specific areas in the anterior vaginal wall. Conversely, as in prostatitis, relapses may occur months or years later, and at that time the specific findings on physical examination will also return.

Anatomic Studies

We obtained several specimens of female urethra and its surrounding soft tissue en bloc from brain-dead donors undergoing harvesting of multiple organs for transplantation. Serial sections, transverse and longitudinal, consistently revealed the presence of the paraurethral glands and confirmed the positive staining for PSA. One case of an older woman who died of a sudden cerebral hemorrhage serendipitously yielded examples of paraurethral glands with active inflammation (Figure 3). The appearance would be parallel to that seen in the histologic examination of a biopsy specimen in a case of prostatitis.

Because prostatitis is capable of raising the systemic blood level of PSA in men, we tested to see if women affected with severe inflammation of the paraurethral glands would reflect an elevation of PSA levels in their blood. Blood specimens taken before and after palpation of the tender glands were studied by an ultrasensitive

Figure 3.—A cross-section of paraurethral glands obtained from a cadaver organ donor is shown. Submucosal and luminal inflammation was demonstrated (**left arrow**). Reactivity with anti–prostate-specific-antigen antibody is absent in the inflamed gland but well shown in 2 adjacent smaller glands (**right arrows**). (Immunoperoxidase stain with hematoxylin counterstain, original magnification × 125.)

PSA immunoassay (Abbott Laboratories, Chicago, Ill), but in all the PSA was undetectable.

Conclusion

In retrospect, it seems likely that clinicians have been overlooking specific infections of the microscopic female paraurethral gland and labeling such cases as the urethral syndrome. Such female prostatitis is common and should be diagnosed by a careful pelvic examination by the initial examining physician or other trained medical personnel. Treatment commensurate with the extraurinary location of the inflamed tissue, as in the male prostate, will give gratifying results, and its success can then be confirmed objectively by reexaminations. The finding and treatment of female prostatitis may eliminate a large portion of the cases of urethral syndrome and abrogate the condescending management of such women with either dilations or anxiolytic drugs.

REFERENCES

1. Gallagher GJA, Montgomerie JZ, North JDK: Acute infections of the urinary tract and the urethral syndrome in general practice. Br Med J 1965; 1: 622-662

2. Messing EM: Urethral syndrome, *In* Walsh PC, Gittes RF, Perlmutter AD, Stamey TA (Eds): Campbell's Urology. Philadelphia, Pa, WB Saunders, 1986, pp 1087-1091

3. Drach GW, Fair WR, Meares EM, Stamey TA: Classification of benign diseases associated with prostatic pain: Prostatitis or prostatodynia? (Letter) J Urol 1978; 120:266

4. de Graaf R: De mulerium organis generationi inserventibus tractatus novus, demonstrans tam homines et animalia caetera omina, quac vivipara dicuntur, haud minus quam ovipara ab ovo originem ducere. Leyden, The Netherlands, 1672, 66

5. Skene AJC: The anatomy and pathology of 2 important glands of the female urethra. Am J Obstet 1880; 13:265

6. Huffman JW: The detailed anatomy of the paraurethral ducts in the adult human female. Am J Obstet Gynecol 1948; 55:86-100

7. Huffman JW: Clinical significance of the paraurethral ducts and glands. Arch Surg 1951; 62:615-626

8. Cabot H, Shoemaker R: Role of glands of the female urethra in the production of infection of the urinary tract. Trans Am Assoc Genitourin Surg 1936; 29:461-472

9. Kerr WS, Leadbetter GW, Donahue J: An evaluation of internal urethrotomy in female patients with urethral or bladder neck obstruction. J Urol 1966; 95:218-221

10. Richardson FH: External urethroplasty in women: Technique and clinical evaluation. J Urol 1969; 101:719-723

11. Evans AT: Etiology of urethral syndrome: Preliminary report. J Urol 1971; 105:245-250

12. Rieser C: A new method of treatment of inflammatory lesions of the female urethra. JAMA 1968; 204:86-92

13. Longo VJ: The female prostate. Urology 1982; 20:108-109

14. Pollen JJ, Dreilinger A: Immunohistochemical identification of prostatic acid phosphatase and prostate specific antigen in female periurethral glands. Urology 1984; 23:303-304

15. Tepper SL, Jagirdar J, Heath D, Geller SA: Homology between the female paraurethral (Skene's) gland and the prostate—Immunohistochemical demonstration. Arch Pathol Lab Med 1984; 108:423-425

16. Holland JM: Prostatic hyperplasia and neoplasia in female *Praomys (Mastomys) natalensis*. J Natl Cancer Inst 1970; 45:1229-1232

17. Jantos C, Altmannsberger M, Weidner W, Schiefer HG: Acute and chronic bacterial prostatitis due to *E coli*: Description of an animal model. Urol Res 1990; 18:207-211

18. Svanholm H, Andersen OP, Røhl H: Tumour of female paraurethral duct—Immunohistochemical similarity with prostatic carcinoma. Virchows Arch [A] 1987; 411:395-398

19. Spencer JR, Brodin AG, Ignatoff JM: Clear cell adenocarcinoma of the urethra: Evidence for origin within paraurethral ducts. J Urol 1990; 143:122-125

20. Zaviačič M, Sidlo J, Borovský M: Prostate specific antigen and prostate specific acid phosphatase in adenocarcinoma of Skene's paraurethral glands and ducts. Virchows Arch A Pathol Anat Histopathol 1993; 423:503-505

21. Karram MM: The painful bladder: Urethral syndrome and interstitial cystitis. Curr Opin Obstet Gynecol 1990; 2:605-611

22. Schmidt RA, Tanagho EA: Urethral syndrome or urinary tract infection? Urology 1981; 18:424-427

23. Kaplan WE, Firlit CF, Schoenberg HW: The female urethral syndrome: External sphincter spasm as etiology. J Urol 1980; 124:48-49

24. Zufall R: Ineffectiveness of treatment of urethral syndrome in women. Urology 1978; 12:337-339

25. Stamm WE, Wagner KF, Amsel R, et al: Causes of the acute urethral syndrome in women. N Engl J Med 1980; 303:409-415

26. Stamm WE, Running K, McKevitt M, Counts GW, Turck M, Holmes KK: Treatment of the acute urethral syndrome. N Engl J Med 1981; 304:956-958

27. Maskell R: Pathogenesis of the urethral syndrome. J R Coll Gen Pract 1988; 38:473-478

28. Cardon CC, Osborne D, Segura JW: Psychologic characteristics of patients with female urethral syndrome. J Clin Psychol 1979; 35:312-313

29. Bernstein AM, Phillips HC: A psychophysiological evaluation of female urethral syndrome: Evidence for a muscular abnormality. J Behav Med 1992; 15:299-312

30. Sugaya K, Nishizawa O, Noto H, et al: [Vesical ultrasonography and internal examination of female patients with urethral syndrome.] Nippon Hinyokika Gakkai Zasshi 1992; 83:1094-1110 (Engl Abstr)

31. Andriole VT: Clinical overview of the newer 4-quinolone antibacterial agents, *In* The Quinolones. London, England, Academic Press, 1988, pp 155-200

Epitomes

Important Advances in Clinical Medicine

Internal Medicine

Kouichi R. Tanaka, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in internal medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Internal Medicine of the California Medical Association, and the summaries were prepared under the direction of Kouichi R. Tanaka, MD, and the panel.

Advances in Lung Transplantation

LUNG TRANSPLANTATION is a successful and recognized option for patients with end-stage lung disease. Clinical disorders that may require lung transplantation include emphysema, pulmonary fibrosis (including sarcoidosis), cystic fibrosis, and pulmonary hypertension (both primary and secondary). Improved immunosuppressive agents, refined surgical techniques, and the institution of prophylactic regimens against infectious diseases have prolonged survival. The acceptance of the efficacy of lung transplantation has resulted in a long list of candidates waiting to receive new lungs. Unfortunately, the donor pool remains stagnant. Many candidates wait for more than a year before they receive new lungs; about a third do not survive the wait.

The recently developed procedure of donor lobectomy has helped to increase the donor lung pool and reduce the waiting period for selected, severely ill patients who would not live long enough to receive cadaveric lungs. For some time, harvesting organs from living donors has been successful with kidney transplantation. Living donor lung transplantation, however, initially was met with intense criticism. The possible concerns, including the risk imposed on the donors, the fears of financial gain, and the strong emotional bonds that may distort judgment, were recognized early. These fears have been allayed by the establishment of strict guidelines to ensure the utmost safety for the donors and recipients. Additional criteria for living donors guarantee that the donors are not coerced, that they do not have substantial psychosocial difficulties, and that they have a normal medical state. To date, 60 donor lobectomies for 30 recipients have been done without donor mortality. One-year survival rates for the recipients are currently 70%, which is comparable to patient survival with cadaveric transplants.

Since the mid-1980s, the combination of cyclosporine, azathioprine, and prednisone has been the mainstay of immunosuppressive treatment to prevent organ rejection. Despite this regimen, acute rejection occurs at least once in about 60% of the recipients and develops between 1 and 12 weeks after transplantation. Chronic rejection usually develops between 8 and 12 months after transplantation in 30% to 40% of the long-term survivors. The sine qua non of chronic rejection is bronchiolitis obliterans, which presents with dyspnea, a clear chest radiograph, and progressive airway obstruction. Treatment involves augmented corticosteroids, antilymphocytic agents (antilymphocyte globulin, OKT-3), or both. Cytotoxic agents (such as methotrexate and cyclophosphamide) and, sometimes, total lymphoid irradiation are also used to treat long-term rejection. Therapeutic intervention, although effective in the acute stage of rejection, has been discouraging for long-term rejection, and the prognosis is poor, particularly if treatment is not instituted early.

Two recently released immunosuppressive agents appear promising. Cyclosporine is a T cell–specific fungal macrolide that has been used since 1981. Because of its lipophilic properties, however, the metabolite is stabilized in an oil-based carrier, and its absorption is variable and sometimes incomplete. This leads to erratic serum concentrations that can result in suboptimal immunosuppression and a greater risk of graft loss or rejection. A new microemulsion of cyclosporine, Neoral, provides improved hydrophilic properties and more consistent absorption and bioavailability. Studies in normal volunteers and renal, liver, and lung transplant recipients have confirmed its effectiveness, its improved pharmacokinetic profiles, and its more consistent absorption. This preparation also has less intrapatient variability. All of this should lead to reduced episodes of graft rejection and possibly improved patient outcome. Tacrolimus is another new agent with similar actions to cyclosporine. Studies in liver, kidney, and lung transplant recipients have shown fewer episodes of rejection when compared with cyclosporine-based primary immunosuppression and a positive outcome when used for rescue therapy.

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REFERENCES

Barbers RG: Lung transplantation in interstitial lung disease. Curr Opin Pulmon Med 1995; 1:401-405

Cohen RG, Barr ML, Schenkel FA, DeMeester TR, Wells WJ, Starnes VA: Living-related donor lobectomy for bilateral lobar transplantation in patients with cystic fibrosis. Ann Thorac Surg 1994; 57:1423-1428

Griffith BP, Bando K, Hardesty RL, et al: A prospective randomized trial of FK506 versus cyclosporine after human pulmonary transplantation. Transplantation 1994; 57:848-851

Starnes VA, Barr ML, Cohen RG: Lobar transplantation—Indications, technique, and outcome. J Thorac Cardiovasc Surg 1994; 108:403-411

UNOS: 1994 Center Specific Report: Lung Data—Overall Survival Rates. UNOS Update 1995; 11:33-36

Clinical Uses for Low-Molecular-Weight Heparins

ALTHOUGH WIDELY USED in Europe for a decade, low-molecular-weight (LMW) heparins have only recently entered the United States market. In relation to prophylaxis and the treatment of thromboembolism, they represent the newest pharmacologic advance since the introduction of warfarin. Low-molecular-weight heparins are degradation products produced by the depolymerization of standard unfractionated heparin. The resulting smaller molecular size produces several favorable pharmacologic features. Because they are not as firmly bound to proteins and to endothelial cells, they have excellent bioavailability following subcutaneous administration, leading to a plasma half-life two to four times longer than that of standard heparin. Through their binding mechanism with antithrombin III, their preferential affinity for factor X compared with factor II results in less prolongation of the activated partial thromboplastin time (aPTT). Hemorrhagic risk is reduced by less platelet interaction and by diminished microvascular permeability. In addition, LMW heparins have demonstrated a lower risk of heparin-induced thrombocytopenia.

Because the half-dozen commercially available LMW heparins are prepared through different depolymerization techniques with varying molecular size and antithrombotic characteristics, they should not be considered pharmacologically and clinically equivalent. The first LMW heparin approved for use in the United States was enoxaparin sodium. It is currently used for deep venous thrombosis prophylaxis following total hip or knee replacement and is administered in a fixed-dose regimen of 3,000 IU subcutaneously twice a day, starting 12 to 24 hours postoperatively and continued for 7 to 14 days. The newest entry into the market is dalteparin sodium, which is used for deep venous thrombosis prophylaxis in at-risk patients undergoing an abdominal operation, with the first dose of 2,500 IU administered one to two hours preoperatively and once a day thereafter.

The important role of LMW heparins in deep venous thrombosis prophylaxis has been highlighted by the recently published guidelines of the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy. Low-molecular-weight heparins have emerged as a recommended pharmacologic agent in every category of deep venous thrombosis prophylaxis with the exception of intracranial neurosurgery. Their primary focus has been in thrombosis prophylaxis following major joint replacement. These patients have an incidence of deep venous thrombosis as high as 70%, with pulmonary embolism being the leading cause of death following elective total hip replacement. Low-molecular-weight heparin is the pharmacologic agent of choice for deep venous thrombosis prophylaxis following total knee arthroplasty. The attractive features of LMW heparins for clinicians are that they are administered in a fixed-dose regimen and do not require the cumbersome and time-consuming laboratory monitoring associated with warfarin therapy. They have also been used in patients with unstable angina and in the prevention of restenosis following coronary artery angioplasty and stent placement. In the latter instance, the use of LMW heparin appears to shorten the duration of hospital stays. Although LMW heparins are more costly than unfractionated heparin or warfarin, several studies have indicated that they may overall be the most cost-effective agent because of reduced laboratory monitoring, invasive testing, and subsequent hospital admissions. As more LMW heparins appear in the United States, market forces should lead to more competitive pricing.

The most exciting future for LMW heparins is in the treatment of deep venous thrombosis. Currently the standard approach to patients with this disorder necessitates five days of hospital stays for the administration of heparin by continuous intravenous infusion, adjusted most commonly by aPTT. Because of their excellent bioavailability and predictable anticoagulant response following subcutaneous administration and because monitoring of laboratory coagulation measures is not required, LMW heparins offer the potential for outpatient treatment of deep venous thrombosis. A recent meta-analysis of ten clinical trials using various LMW heparins compared with standard heparin in the initial treatment of deep venous thrombosis showed statistically significant reductions for symptomatic thromboembolic complications, clinically important bleeding, and mortality. Encouraging data from a recent Canadian trial found enoxaparin to be effective and safe in the outpatient treatment of deep venous thrombosis. If results from larger ongoing trials prove beneficial, we may be able to substantially reduce the length of stay or even eliminate many of the 300,000 hospital admissions each year for this disorder.

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REFERENCES

Bergvist D, Matzsch T: Cost/benefit aspects of thromboprophylaxis. Haemostasis 1993; 23(suppl):15-19

Clagett GP, Anderson FA, Heit J, Levine MN, Wheeler HB: Prevention of venous thromboembolism. Chest 1995; 108:312S-334S

Lensing AW, Prins MH, Davidson BL, Hirsh J: Treatment of deep venous thrombosis with low-molecular-weight heparins—A meta-analysis. Arch Intern Med 1995; 155:601-607

Levine M, Gent M, Hirsh J, et al: A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334:677-681

Saltiel E, Shane R: Evaluating costs of a pharmacist-run thromboprophylaxis program. Formulary 1996; 31:276-290

Warkentin TE, Levine MN, Hirsh J, et al: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330-1335

Exercise-Induced Asthma

ALTHOUGH THE CAUSES of exercise-induced asthma are still unknown, there are two theories that are best supported by clinical observation. One postulates that exercise leads to water loss in the airways, inducing the release of inflammatory mediators that stimulate bronchospasm. The second theorizes that cooling of the airways by exercise causes changes in blood flow in the bronchial circulation that also induce the release of bronchospastic mediators.

Three classes of drugs have been adopted by the International Olympic Committee for exercise-induced asthma: agonists, cromolyn sodium, and theophylline. Aerosolized steroids have not been shown to be helpful in exercise-induced asthma unless administered over a four-week period before exercise. Theophylline has been effective only in patients who use it long term. Recent studies have attempted to establish the efficacy of experimental longer-acting β_2-agonists and cromolyn in exercise-induced asthma. One showed improved protection from this disorder when using long-acting cromolyn and nedocromil compared with cromolyn alone.

Although we still have much to learn about it, the following is recommended for the management of exercise-induced asthma. The diagnosis is made by showing a 15% fall in the forced expiratory volume in one second or the peak expiratory flow rate monitoring at 0, 3, 5, 10, 15, or 20 minutes after 6 minutes of strenuous exercise. Specific information from the history, obtaining positive histamine or methacholine challenge tests, or demonstrating adequate responses to therapeutic trials of drugs effective in treating exercise-induced asthma can also help make the diagnosis.

Most persons who suffer from exercise-induced asthma respond to two inhalations of a β_2-agonist (short or long acting) administered five to ten minutes before exercise. Salmeterol (long-acting β-agonist) seems to provide longer protection than the shorter-acting β-agonists (albuterol). For more difficult cases, prolonged protection can be obtained by combining cromolyn or nedocromil with β_2-agonists. No difference in efficacy was found between cromolyn and nedocromil, and therefore, either one can be used. A trial of ipratropium bromide in metered-dose inhalant form, in combination with β_2-agonists or cromolyn sodium or both, can be of some benefit. Both β_2-agonists and cromolyn sodium are available in metered-dose inhalers, in capsule form specifically designed for spinhalers, and in solutions for nebulization. The oral administration of β_2-agonists has not been effective in the treatment of exercise-induced asthma.

For those patients with more severe exercise-induced asthma, it is recommended to choose a sport that requires less exertion—that is, swimming, downhill skiing, and recreational cycling as opposed to running, cross-country skiing, and bicycle racing. It is also recommended to undergo a brief warm-up period before engaging in more intense exercise and a warm-down after completing exercise. The abrupt onset and sudden cessation of exercise puts persons more at risk for exercise-induced asthma. Finally, patients who have exercise-induced asthma and who are sensitive to airborne pollens should not undergo strenuous exercise outdoors during the high-pollen season.

Several additional factors are known to exacerbate the response to exercise in patients with asthma and should be kept in mind in the prevention of this disorder. The more severe the underlying asthma, the greater the adverse response to exercise in asthma. The longer the duration of exercise, the greater the risk of it inducing asthma (this applies to the intensity of exercise as well). Exercise-induced asthma is much more likely to be provoked in cold and dry weather conditions.

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REFERENCES

de Benedicts, Tuteri G, Pazzelli A, Bertotto A, Bruni L, Vacarro R: Cromolyn versus nedocromil: Duration of action in exercise-induced asthma in children. J Allergy Clin Immunol 1995; 4:510-514

Inman MD, O'Byrne PM: The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med 1996; 1:65-69

Kemp JP, Dockhorn RJ, Busse WW, Bleecker ER, Van As A: Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. Am J Respir Crit Care Med 1994; 150:1612-1615

Woolley M, Anderson SO, Quigley BM: Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. Chest 1990; 9:39-45

Wright LA, Martin RJ: Nocturnal asthma and exercise-induced bronchospasm: Why they occur and how they can be managed. Postgrad Med 1995; 6:83-90

Osteoporosis—New Techniques for Screening, Diagnosis, and Clinical Monitoring

OSTEOPOROSIS is a major public health problem that already affects 25 million Americans, is responsible for about 1.5 million fractures annually, and has been estimated to result in direct and indirect health care expenditures of $10 billion annually. The National Osteoporosis Foundation estimates that half of all women older than 50 years will have an osteoporosis-related fracture. Men are also at risk, with a 5% lifetime risk of hip fracture.

Bone is continuously resorbed and formed throughout life in the process of remodeling or turnover. After ages 30 to 40, resorption exceeds formation, resulting in net bone loss in older women and men. In perimenopausal women, estrogen deficiency results in more rapid bone loss for five to ten years after menopause. Osteoporosis occurs when bone loss is sufficient to cause mechanical weakness and increased risk of fracture. Bone loss cannot be reversed, but the likelihood of complications can be minimized by identifying patients, even older ones with high rates of bone turnover and low bone density, and by intervening to slow or stop net bone loss.

The incidence of osteoporosis is expected to rise even further as the population ages. It is, therefore, imperative to identify the persons most at risk for bone loss and fracture. Risk factors and causes of secondary osteoporosis, such as hyperthyroidism, hyperparathyroidism, or treatment with

glucocorticoids, should be searched for during the initial patient evaluation. Because osteoporosis is the result of a process that continues for the life of the patient, physicians must remain alert to the development of contributing factors during long-term follow-up as well. The routine history and physical examination are useful in discovering these disorders. For instance, the history may reveal primary or secondary amenorrhea, alcohol and cigarette use, drug treatment, dietary habits, gastric or intestinal resections, sunlight deprivation, and immobilization. Physical examination may suggest such conditions as hyperthyroidism or glucocorticoid excess. Screening laboratory tests, such as complete blood count, chemistry panel, erythrocyte sedimentation rate, urinalysis, and serum and urine protein levels may suggest endocrine, gastrointestinal, or renal disease or cancer. In these cases, specific diagnoses should be established and addressed as soon as possible.

Should risk factors and the initial clinical assessment indicate a strong likelihood of osteoporosis, bone mineral density can be established with bone densitometry. Bone turnover rate and the risk of further bone loss can be determined by measuring biochemical indices of bone resorption and formation. Measuring the bone mineral density is useful in assessing current bone mass and establishing baselines for follow-up. It correlates with bone strength: low bone mineral density is associated with fracture risk. The use of dual-energy x-ray absorptiometry has made accurate and reproducible bone mineral density measurements possible for several years.

Bone density alone, however, cannot predict future changes in bone tissue. Dynamic measurements of the bone remodeling process, made possible by recent breakthroughs in immunoassay technology, now offer the potential of stratifying the risk of future bone loss, determining the need for treatment, and monitoring the efficacy of treatment over time. The rate of bone turnover can be assessed by measuring levels of one or more of the biochemical markers associated with bone resorption and formation that are released into the blood or urine. Testing for biochemical markers is noninvasive and relatively inexpensive.

New immunoassays for biochemical bone markers are now reaching clinical laboratories. The pyridinium crosslinks of collagen, deoxypyridinoline, pyridinoline, and their associated peptides, measured in urine, are newly recognized markers for bone resorption that are highly sensitive and specific for the degradation of bone collagen. Bone-specific alkaline phosphatase and osteocalcin are serum markers that have good sensitivity and specificity for bone formation. Together, the measurement of pyridinium crosslinks and bone-specific alkaline phosphatase or osteocalcin provide an index of bone turnover rate. The clinical usefulness of these new techniques is twofold. They identify adults at high risk for the development of osteoporosis or older adults with established osteoporosis but continued high rates of bone loss, so that aggressive therapy can be instituted to prevent or limit the disorder. They also provide a noninvasive, sensitive, and dynamic tool for monitoring the clinical course and effect of therapy.

Whether evaluating a perimenopausal woman or treating an older man with osteoporosis, a similar assessment and follow-up algorithm can be followed. The baseline measurement of pyridinium crosslinks and a bone formation marker along with bone mineral density may determine the current and future risks of fracture and bone loss. The initiation of a suitable antiresorptive therapy, such as hormone replacement, calcitonin, or bisphosphonate, appropriate for the patient and condition can then be undertaken. Progress should be checked within three months to verify efficacy and compliance. Thereafter, annual bone mineral density and bone marker measurements are used as monitors. By allowing better management of bone loss and osteoporosis, these new tools in clinical medicine provide the opportunity to prevent or decrease morbidity, mortality, and health care costs and retain or improve the quality of patients' lives.

Editor's Note: The author has a financial interest in a small, public company that researches, develops, and commercializes improved diagnostic methods for managing bone diseases. This company's current and future products measure some of the compounds mentioned in this epitome.

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REFERENCES

Delmas PD: Biochemical markers for the assessment of bone turnover, *In* Riggs BE, Melton LJ, III (Eds): Osteoporosis: Etiology, Diagnosis, and Management. Philadelphia, Pa, Lippincott-Raven, 1995, pp 319-333

Riggs BL, Melton LJ III: The worldwide problem of osteoporosis: Insights afforded by epidemiology. Bone 1995; 17:505S-511S

Renal Complications of Hepatitis C Virus Infection

Infection with the hepatitis C virus (HCV) has recently been implicated in the pathogenesis of several extrahepatic disorders, notably mixed cryoglobulinemia and cryoglobulinemic glomerulonephritis. The HCV, an RNA virus, is transmitted by blood products, injection drug abuse, sexual contact, or vertical transmission. Although acute hepatitis C is usually mild and anicteric, the infection leads to chronic hepatitis in at least 50% of cases and chronic active hepatitis, cirrhosis, or hepatocellular carcinoma in about 10% of all cases.

Once established, spontaneous resolution of HCV viremia is unusual. Furthermore, HCV can replicate in extrahepatic sites (such as peripheral blood mononuclear cells). Chronic antigenic stimulation and persistent viral replication cause polyclonal B-lymphocyte proliferation, antiglobulin immunoglobulin (Ig) M antibody (rheumatoid factor) production, and type III mixed cryoglobulinemia in about a third of patients with chronic hepatitis C. A smaller percentage of patients exhibit a monoclonal B-lymphocyte proliferation and monoclonal IgM rheumatoid factor production resulting in type II mixed cryoglobulinemia.

Hepatitis C infection is now recognized as a major cause of mixed cryoglobulinemia. Circulating HCV RNA or HCV antibodies (or both) are detectable in the serum of most patients with type III and virtually all patients with type II mixed cryoglobulinemia, as compared with less than 1% of the general population. Nearly all circu-

lating HCV RNA in these patients is contained in cryoprecipitable immune complexes. Clinically, types II and III mixed cryoglobulinemia share a common syndrome characterized by weakness, arthralgia, purpura (due to leukocytoclastic vasculitis), Raynaud's phenomenon, and peripheral neuropathy. Renal involvement is uncommon in type III mixed cryoglobulinemia, but is common in type II mixed cryoglobulinemia, with glomerulonephritis developing in more than 50% of patients.

The most common renal lesion associated with mixed cryoglobulinemia is membranoproliferative glomerulonephritis type I. Patients with membranoproliferative glomerulonephritis type I typically present with proteinuria and microhematuria. Mild to moderate renal insufficiency is present in about 50% and the nephrotic syndrome in about 25% of the cases.,The course of the renal disease is unpredictable, with partial or complete remission, persistent urinary abnormalities without renal insufficiency, and intermittent exacerbations and remissions each occurring in approximately a third of the affected patients. Rarely, acute glomerulonephritis with oliguric renal failure occurs. Chronic renal failure occurs in less than 10% of cases, usually after prolonged periods.

Laboratory findings include type II cryoglobulinemia (monoclonal IgM), C4 hypocomplementemia, and occasional C3 hypocomplementemia. Antinuclear and antineutrophil cytoplasmic antibodies are typically absent. Hepatitis C virus serologic tests should be obtained in all patients with membranoproliferative glomerulonephritis even in the absence of circulating cryoglobulins or discernible liver disease, as these features are frequently absent at the time of the initial evaluation.

Light-microscopic examination of a renal biopsy usually reveals mesangial proliferation, accentuated lobulation of the glomerular tuft, and double-contoured glomerular basement membranes. Occasionally a patient may have exudative glomerulonephritis, focal glomerulosclerosis, or membranous nephropathy. Immunofluorescent microscopy usually reveals mesangial and capillary deposits of IgM, IgG, and C3. Subepithelial immune deposits consistent with type III membranoproliferative glomerulonephritis or sparse immune deposits similar to acute exudative and proliferative glomerulonephritis are occasionally encountered.

Several histologic features may differentiate the cryoglobulinemic form of membranoproliferative glomerulonephritis from the idiopathic form. For example, the glomerular capillary lumens may be filled with deposits that display the ultrastructural features of cryoglobulins, such as granular or fibrillar structures and possibly virus-like particles. Other findings include massive monocyte infiltration, endocapillary proliferation, vasculitis of small and medium-size renal arteries, and extensive capillary wall abnormalities.

A growing body of evidence suggests that HCV infection underlies nearly all cases of cryoglobulinemic glomerulonephritis. A plausible theory for the pathogenesis of the renal lesion is that HCV-IgG antibody complexes are bound by the monoclonal IgM rheumatoid factor, which has a strong affinity for the glomerular basement membrane and mesangial matrix.

Treatment

Interferon alfa (IFN-α) inhibits HCV replication and, as such, can be effective in the treatment of chronic hepatitis C infection. A six-month course of IFN-α (3 million units 3 times a week) has been shown to reduce viremia and improve liver function and histologic features in 50% of patients. The disease frequently relapses following the cessation of therapy, however.

Several studies have suggested that IFN-α therapy may improve extrahepatic complications of HCV infection, specifically mixed cryoglobulinemia and membranoproliferative glomerulonephritis. Interferon alfa therapy reduces serum HCV RNA to undetectable levels in most patients with mixed cryoglobulinemia, lowers circulating levels of cryoglobulin and rheumatoid factor, and lessens clinical symptoms such as purpura and arthralgias. Viremia and cryoglobulinemia almost always recur, however, after therapy is discontinued.

About half the patients with HCV-associated membranoproliferative glomerulonephritis exhibit a substantial reduction in proteinuria with an increase in the glomerular filtration rate following IFN-α therapy. The greatest clinical response is seen in patients showing the disappearance of HCV viremia. Viremia and proteinuria generally recur after the cessation of therapy, however.

Interferon alfa is usually well tolerated. Its common side effects include a flulike illness, insomnia, and malaise. In addition, peripheral neuropathy may transiently worsen in patients with mixed cryoglobulinemia, and proteinuria may rarely increase during therapy. The average wholesale drug price for a six-month course of IFN-α is about $850. Despite the relatively high cost of the drug, recent studies concluded that IFN-α is cost-effective for chronic HCV hepatitis.

In patients with severe extrahepatic manifestations, plasmapheresis and immunosuppressive therapy using prednisone and cytotoxic agents such as cyclophosphamide or chlorambucil has had some success. Large-scale controlled studies of these therapies are lacking, however. High doses of intravenous methylprednisolone sodium succinate have been reported to improve renal function and proteinuria in patients with HCV-associated acute glomerulonephritis, despite the persistence of viremia and cryoglobulinemia.

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REFERENCES

D'Amico G, Fornasieri A: Cryoglobulinemic glomerulonephritis: A membranoproliferative glomerulonephritis induced by hepatitis C virus. Am J Kidney Dis 1995; 25:361-369

Johnson RJ, Willson R, Yamabe H, et al: Renal manifestations of hepatitis C virus infection. Kidney Int 1994; 46:1255-1263

Roth D: Hepatitis C virus: The nephrologist's view. Am J Kidney Dis 1995; 25:3-16

New Treatments of Sickle Cell Disease

DESPITE IMPROVED treatment of sickle cell disease, there is no widely available cure. This encourages continued emphasis on prenatal diagnosis. The polymerase chain reaction (PCR) has provided improved methods for detecting sickle cell genes in fetal DNA obtained by chorionic villus sampling or amniocentesis. One PCR method, reverse dot blotting, can screen in a single reaction for the several genes that cause sickle cell disease—hemoglobin (Hb) S, Hb C, and all the β-thalassemia alleles of African Americans.

In persons with sickle cell disease, transfusions are a traditional approach. Indications are now better understood and include the imminent dangers of hypoxemia or acidosis for which partial exchange in adults or children is indicated. A need exists for improved blood rheology to prevent recurrent strokes or to treat priapism, which often require simple or partial exchange transfusion. Pain crisis is not an indication for transfusions, nor is prophylactic transfusion necessary in pregnancy. Simple transfusion before an operation is as good as more aggressive partial exchange and entails fewer complications. The controversy over the use of preoperative transfusion versus no transfusion at all will be resolved only with a randomized trial.

Hemoglobin F protects against the ravages of sickle cell disease because it inhibits Hb S polymerization. Pharmacologic agents that increase Hb F production include arginine butyrate, which appears to have limited therapeutic benefit in sickle cell disease, and hydroxyurea, which in adults substantially decreases the severity of anemia and the frequency of pain crisis, acute chest syndrome, hospital admission, and transfusion. The questions of long-term risks in adults and of efficacy and short- and long-term risks in children are unanswered. Many experts recommend administering hydroxyurea at an initial daily oral dose of 15 mg per kg for adults with sickle cell anemia (Hb SS) who have frequent pain or transfusion dependence and who are willing to avoid pregnancy. Bone marrow suppression must be monitored carefully.

The occlusion of sickle cell blood flow is mediated by the adherence of sickle reticulocytes to vascular endothelium, followed by the trapping of poorly deformable, dehydrated sickle erythrocytes. An artificial surfactant (RheothRx) that inhibits the adherence of sickle erythrocytes to endothelial cells was found to reduce the narcotic requirement during painful crises and may soon be available for treating acute painful episodes. The severe dehydration of sickle erythrocytes results from the combined effects of the calcium-sensitive potassium efflux and potassium-chloride cotransport. These may be inhibited, respectively, by the administration of oral clotrimazole and magnesium, which preserve sickle erythrocyte hydration and are under study to ascertain their therapeutic potential.

Bone marrow transplantation for sickle cell disease offers great benefit but substantial risk. Its cost of about $200,000 compares favorably with the approximately $112,000 per year required to care for a transfusion-dependent patient with sickle cell disease. Risk-benefit considerations of the quantity and quality of life reveal that for patients with Hb SS, the life expectancy is in the fifth decade and that pain occurs rarely or never in about a third of patients. An enigma associated with bone marrow transplantation concerns exposing patients in whom severe disease may never develop to the risk of transplantations versus withholding possible cure from patients until they have a potentially disabling complication. Of 22 children with severe sickle cell disease treated with bone marrow transplantation, 20 are alive, 17 with stable donor engraftment. Survival and event-free survival are 88% and 75%, respectively. A greater use of bone marrow transplantation for sickle cell disease will depend on continued improvement in methods and will probably be confined largely to children.

Correcting the expression of or replacing the sickle cell gene has become a real possibility. The greatest success in achieving the goals of safe, efficient, and stable transfer of a normal globin gene into hematopoietic stem cells has been with the use of the adenoassociated virus (AAV) as a vector. This virus does not cause human disease, integrates transgenes into the host genome, accommodates high-level expression, and infects a wide variety of human cells. The transfection of human erythroleukemia cells with AAV containing a human γ-globin gene linked to an HS-2 promoter resulted in normal regulation and a high-level expression of γ-globin. Similar approaches to gene therapy are predicted to provide effective therapy for sickle cell disease soon.

Increased understanding of sickle cell disease pathophysiology has led the way to a variety of new therapeutic interventions. The clinical approach to this disease soon will be greatly changed as the result.

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REFERENCES

Adams-Graves P, RheothRx Sickle Cell Study Group: RheothRx® (Poloxomer 188) injection for the acute painful episode of sickle cell disease (SCD): A pilot study (Abstr). Blood 1994; 84(suppl 1):1625A

Charache S, Terrin ML, Moore RD, et al: Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 1995; 332:1317-1322

Embury SH, Hebbel RP, Mohandas N, Steinberg MH: Sickle Cell Anemia: Basic Principles and Clinical Practice. New York, NY, Raven Press: Medical and Scientific Publishers, 1994

Sher GD, Ginder GD, Little J, Yang S, Dover GJ, Olivieri NF: Extended therapy with intravenous arginine butyrate in patients with β-hemoglobinopathies. N Engl J Med 1995; 332:1606-1610

Vichinsky EP, Haberkem CM, Neumayr L, et al: A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. N Engl J Med 1995; 333:206-213

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Alerts, Notices, and Case Reports

Thrombotic Thrombocytopenic Purpura Associated With Histamine H_2-Receptor Antagonist Therapy

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FIRST DESCRIBED in 1924, thrombotic thrombocytopenic purpura (TTP) is an uncommon disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic deficits, renal dysfunction, and fever.[1-3] In this report, we describe a case of TTP associated with the use of famotidine, a histamine H_2-receptor antagonist. To our knowledge, this is the first documented case of TTP due to an H_2-receptor antagonist.

Report of a Case

The patient, a 63-year-old man, was admitted to the hospital because of the acute onset of slurred speech and left-sided weakness on the day of admission. He did not have fever, headache, blurred vision, incontinence, seizures, hematuria, or skin discoloration. A week before his admission, the patient began taking famotidine (20 mg orally once a day) for gastroesophageal reflux symptoms. His medical history was relevant for an episode of TTP 14 years before this admission during which he was taking cimetidine for peptic ulcer disease. This earlier episode of TTP began about five weeks after the initiation of cimetidine therapy, and the TTP resolved completely after steroid therapy, blood transfusion, and the discontinuation of cimetidine.

On admission, the patient's temperature was 37.2°C (99°F), his pulse rate was 84 beats per minute, and his blood pressure was 170/80 mm of mercury. On physical examination, the patient had slurred speech and mild weakness in his left leg; the rest of the physical and neurologic findings were unremarkable. Pertinent laboratory studies included a complete blood count showing a hematocrit of 0.219 (21.9%) with a reticulocyte fraction of 0.134 (13.4%) and a platelet count of 14×10^9 per liter (14,000 per μl); a peripheral blood smear showing pronounced anisopoikilocytosis, including numerous nucleated erythrocytes, schistocytes, helmet cells, tear drop cells, and fragmented erythrocytes; total serum bilirubin level, 34 μmol per liter (2 mg per dl) (normal, 3.4 to 20.5 μmol per liter); serum lactate dehydrogenase (LDH) level, 1,207 units per liter (normal 100 to 225 units per liter); and urinalysis showing 2+ blood. The remainder of blood chemistry tests, liver function tests, and coagulation studies (including fibrinogen and fibrin-split products) were within normal limits; a direct Coombs' test was negative. An emergency computed tomographic scan of the head revealed no acute infarction or hemorrhage. A subsequent bone marrow biopsy revealed pronounced normocytic erythroid hyperplasia, a substantial increase in the number of megakaryocytes, maintenance of a trilineage maturation pattern, and no evidence of any infiltrative processes. Thus, a diagnosis of TTP was made.

The patient was treated with corticosteroids, the transfusion of red blood cells, and daily plasmapheresis with fresh-frozen plasma, in addition to the discontinuation of famotidine. His hospital course was uncomplicated, with gradual and complete resolution of his neurologic signs and hematologic abnormalities over several days. He was well and asymptomatic with no recurrence of any neurologic problems at one-year follow-up.

Discussion

Thrombotic thrombocytopenic purpura is more common in women than men by a ratio of 3:2 and occurs most often in the third decade of life.[3,4] The onset of symptoms in patients with TTP is typically abrupt.[2] About 30% of patients present with the five characteristic manifestations, whereas 70% to 80% of patients present with thrombocytopenia, hemolytic anemia, and neurologic dysfunction.[4,5] The most common initial presentations of TTP are neurologic deficits and hemorrhage.[1,2] On laboratory examination, TTP patients show hemolytic anemia and thrombocytopenia. Severe anemia is common, and about 40% of patients have a hemoglobin of 65 grams per liter (6.5 grams per dl) or less.[1,4] Platelet counts are often less than 20×10^9 per liter (20,000 per μl).[4,6] Leukocytosis may be present in about 80% of patients.[3] Peripheral blood smears show schistocytes without spherocytes, consistent with a nonimmune hemolytic anemia.[6] Serum LDH levels are markedly elevated and have been used in conjunction with the platelet count as a marker for disease progression and efficacy of therapy.[2,4,5] Coagulation studies differentiate TTP from disseminated intravascular coagulation (DIC); fibrin-degradation products present in patients with DIC are lacking in those with TTP.[4,7] In addition, prothrombin time, partial thromboplastin time, and fibrinogen values are usually normal in patients with TTP, in contrast to the abnormalities noted in patients with DIC.[4,7]

The clinical manifestations of TTP represent damage to various organ systems due to widespread thrombosis of

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ABBREVIATIONS USED IN TEXT

DIC = disseminated intravascular coagulation
LDH = lactate dehydrogenase
TTP = thrombotic thrombocytopenic purpura

the microvasculature.[2,8] Possible stimuli for intravascular thrombus formation include diffuse endothelial damage and abnormally large von Willebrand factor multimers.[2,6,7] Available data from experimental studies indicate that various noxious stimuli produce endothelial injury, a transient release of platelet-agglutinating factors, and unusually large multimers of factor VIII:von Willebrand factor from injured endothelium, resulting in abnormal platelet aggregation and producing the syndrome of TTP.[6-8] Other factors implicated in the pathogenesis of TTP include impaired fibrinolytic activity, immune complex formation and deposition, abnormalities of endothelial prostacyclin production, and a deficiency in platelet-aggregating factor inhibitor.[2,6,7] An autoimmune cause has also been postulated because TTP has been associated with several autoimmune disorders, including Sjögren's syndrome, polymyositis, systemic lupus erythematosus, and rheumatoid arthritis.[7-9]

Thrombotic thrombocytopenic purpura has also been associated with pregnancy; allograft rejection; vaccines[2]; bacterial, viral, and fungal infections[10]; carcinomas[10]; a dog bite[11]; a beesting[10]; and carbon monoxide poisoning.[12] In addition, the following drugs have been reported to cause this disorder: penicillin,[13] sulfonamides,[10] rifampicin,[14] metronidazole, quinine, cyclosporin,[15] penicillamine,[16] ticlopidine,[17] defibrotide,[18] oral contraceptive agents,[2,10] chemotherapeutic agents,[10,15] and cocaine.[15] A review of the English-language literature between 1966 and 1995 did not reveal any cases of TTP related to H_2-receptor antagonist therapy. Moreover, a computer search of the 1995 Drugdex database revealed that although the use of H_2-receptor antagonists has been associated with various hematologic abnormalities (Table 1), none have been reported to cause TTP.[19] To our knowledge, our patient represents the first documented case of TTP associated with H_2-receptor antagonists. Although the pathogenesis of the hematologic adverse effects associated with H_2-receptor antagonists (Table 1) remains unclear, experimental studies suggest that these adverse effects are probably due to either direct toxicity for various hemopoietic cells or drug-induced immune reaction.[20,21] In the present case, we speculate that the H_2-receptor antagonists cimetidine and famotidine probably initiated endothelial damage and abnormal platelet aggregation, resulting in TTP.

At the time of presentation, our patient was taking no medications other than famotidine. The temporal relationship of the onset of symptoms in our patient correlates with the initiation of famotidine therapy. We speculate that he had TTP 14 years earlier while taking cimetidine, thus the initiation of famotidine seven days before this admission resulted in an inadvertent rechallenge with another H_2-receptor antagonist and recurrence of the TTP. We recognize, however, that about 30% of patients with TTP may have a recurrence during the first ten years after the initial episode[22]; hence, we cannot exclude the possibility that this patient simply had a relapse that was not related to the coincidental use of famotidine.

Finally, the treatment of TTP has been largely empiric. Over the past two decades, plasmapheresis or plasma exchange has become the treatment of choice for this disorder. In the 1960s, the mortality due to TTP was greater than 90%[1,4]; however, the introduction of plasmapheresis and improved supportive care during the past two decades have led to an overall survival rate of greater than 80%.[4,5,15] In a recent prospective trial of 108 patients with TTP treated with plasmapheresis and prednisone, a one-year survival rate of 91% was reported.[23] It remains unclear, however, whether plasmapheresis is effective due to the removal of a harmful substance or to the replacement of a deficient substance. Although plasmapheresis is the current treatment of choice, other adjunctive therapies that have been reported to be effective in individual cases include glucocorticoids, antiplatelet agents (such as aspirin, dipyridamole, sulfinpyrazone, or dextran), prostacyclin infusions, intravenous immune globulin therapy, vincristine sulfate, and splenectomy.[2,6,8] The relative benefit of these adjunctive treatments in conjunction with plasmapheresis or plasma exchange remains uncertain due to the

TABLE 1.—*Hematologic Adverse Effects Associated With Histamine H_2-Receptor Antagonists**

	H_2 Receptor Antagonists			
Hemotologic Toxicity	*Cimetidine*	*Ranitidine*	*Fomotidine*	*Nizatidine*
Agranulocytosis	X	X		
Neutropenia	X	X	X	
Leukopenia		X		X
Eosinophilia	X	X		
Aplastic anemia	X	X		
Pancytopenia	X	X		
Thrombocytopenia	X	X	X	X
Leukemoid reaction		X		
Hemolytic anemia		X		
Anemia				X

*From the Drugdex.[19]

rarity of the disease and the lack of prospective, controlled clinical trials. Heparin use is generally contraindicated in patients with TTP because the thrombotic occlusions are not thrombin-mediated.[24] Platelet transfusions have resulted in fatal cerebral infarction due to platelet aggregates in the brain and are not recommended.[2,25]

REFERENCES

1. Amorosi EL, Ultmann JE: Thrombotic thrombocytopenic purpura: Report of 16 cases and review of the literature. Medicine 1966; 45:139-155

2. Bithell TC: Thrombotic thrombocytopenic purpura and other forms of nonimmunologic platelet destruction, *In* Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (Eds): Clinical Hematology, 9th edition. Philadelphia, Pa, Lea & Febiger, 1993, pp 1356-1361

3. Petitt RM: Thrombotic thrombocytopenic purpura: A thirty year review. Semin Thromb Hemost 1980; 6:350-355

4. Ridolfi RL, Bell WR: Thrombotic thrombocytopenic purpura: Report of 25 cases and review of the literature. Medicine 1981; 60:413-428

5. Thompson CE, Damon LE, Ries CA, Linker CA: Thrombotic microangiopathies in the 1980s: Clinical features, response to treatment, and the impact of the human immunodeficiency virus epidemic. Blood 1992; 80:1890-1895

6. Schmidt JL: Thrombotic thrombocytopenic purpura: Successful treatment unlocks etiologic secrets. Mayo Clin Proc 1989; 64:956-961

7. Ellingson TL, Wilske K, Aboulafia DM: Thrombotic thrombocytopenic purpura in a patient with polymyositis: Therapeutic importance of early recognition and discussion of pathogenic mechanisms. Am J Med Sci 1992; 303:407-410

8. Ruggenenti P, Remuzzi G: Thrombotic thrombocytopenic purpura and related disorders. Hematol Oncol Clin North Am 1990; 4:219-241

9. Noda M, Kitagawa M, Tomoda F, Iida H: Thrombotic thrombocytopenic purpura as a complicating factor in a case of polymyositis and Sjögren's syndrome. Am J Clin Pathol 1990; 94:217-221

10. Kwaan HC: Miscellaneous secondary thrombotic microangiopathy. Semin Hematol 1987; 24:141-147

11. Mars DR, Knochel JP, Cotton JR, Fuller TJ: Thrombotic thrombocytopenia purpura after a dogbite. South Med J 1980; 73:676-678

12. Stonesifer LD, Bone RC, Hiller FC: Thrombotic thrombocytopenic purpura in carbon monoxide poisoning—Report of a case. Arch Intern Med 1980; 140:104-105

13. Parker JC, Barrett DA: Microangiopathic hemolysis and thrombocytopenia related to penicillin drugs. Arch Intern Med 1971; 127:474-477

14. Fahal IH, Williams PS, Clark RE, Bell GM: Thrombotic thrombocytopenic purpura due to rifampicin. BMJ 1992; 304:882

15. George JN, El-Harake M: Thrombocytopenia due to enhanced platelet destruction by nonimmunologic mechanisms, *In* Beutler E, Lichtman MA, Coller BS, Kipps TJ (Eds): Hematology, 5th edition. New York, NY, McGraw-Hill, 1995, pp 1290-1303

16. Ahmed F, Sumalnop V, Spain D, Tobin MS: Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. Arch Intern Med 1978; 138: 1292-1293

17. Page Y, Tardy B, Zeni F, Comtet C, Terrana R, Bertrand JC: Thrombotic thrombocytopenic purpura related to ticlopidine. Lancet 1991; 337:774-776

18. Perotti C, Torretta L, Costamagna L, Salvaneschi L: Thrombotic thrombocytopenic purpura after defibrotide therapy. Haematologica 1994; 79:569

19. Drugdex: Drug evaluations, *In* Gelman CR, Ruimack BH (Eds): Drugdex Information System [online database]. Denver, Colo, Micromedex, Inc, 1995

20. Aymard JP, Aymard B, Netter P, Bannwarth B, Trechot P, Streiff F: Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol 1988; 3:430-448

21. List AF, Beaird DH, Kummet T: Ranitidine-induced granulocytopenia: Recurrence with cimetidine administration. Ann Intern Med 1988; 108:566-567

22. Shumak KH, Rock GA, Nair RC, the Canadian Apheresis Group: Late relapses in patients successfully treated for thrombotic thrombocytopenic purpura. Ann Intern Med 1995; 122:569-572

23. Bell WR, Braine HG, Ness PM, Kickler TS: Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. N Engl J Med 1991; 325:398-403

24. Nalbandian RM, Henry RL: A proposed comprehensive pathophysiology of thrombotic thrombocytopenia purpura with implicit novel tests and therapies. Semin Thromb Hemost 1980; 6:356-390

25. Harkness DR, Byrnes JJ, Lian ECY, Williams WD, Hensley GT: Hazard of platelet transfusion in thrombotic thrombocytopenic purpura. JAMA 1981; 246:1931-1933

Anorectal Melanoma
Successful Palliation in a 59-Year-Old Woman

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ALTHOUGH THE ANUS is the most common site for gastrointestinal melanoma, anorectal melanoma is an uncommon disease, with about 500 reported cases since it was first described by Moore in 1857.[1] The prognosis for melanoma in this location is poor, with five-year survival rates generally less than 10% despite surgical resection. Indeed, survival is often measured in months following diagnosis. The poor prognosis in patients with this disease may be attibutable to the aggressive nature of the tumor as well as its advanced stage at the time of diagnosis. We report a case of advanced anorectal melanoma and review the literature, with special emphasis on the treatment options available to patients with this disease.

Report of a Case

The patient, a 59-year-old woman, presented to the emergency department with weakness, fatigue, weight loss, and intermittent rectal bleeding of several weeks' duration. On physical examination, she was found to have a pigmented lesion on the right lateral aspect of her anus that was large (7 cm × 7 cm), necrotic, fungating, and nontender (Figure 1). There was bleeding from the mass. No hepatomegaly, splenomegaly, or abdominal masses were noted. She had unilateral 3+ pitting edema of her left lower extremity. Laboratory studies revealed a hematocrit of 0.16 (16%), and liver function test results were within normal limits.

The patient was taken to the surgery department for sigmoidoscopic examination under anesthesia. On close examination, the mass was found to arise on the right lateral region of the anal canal and was nearly circumferential. The mass extended 7 cm superiorly into the rectum, with involvement of the anterior, left lateral, and posterior sides. No rectovesical or rectovaginal fistulas were found.

Histopathologic analysis of a biopsy specimen revealed loosely packed sheets of pleomorphic cells, with an abundance of pigment-containing melanotic cells (not shown). The depth of the tumor locally was greater than 3 to 4 mm, which was the maximum depth of the biopsy specimen.

A computed tomographic scan from the lower thorax through the pelvis was obtained that showed the previ-

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ously described anal mass measuring 8 cm craniocaudally and 7 cm in the anteroposterior and lateral dimensions (Figure 2). There was extensive local inflammation, edema, or both around the mass, with possible extension into the levator ani musculature, vagina, and urinary bladder. Small (about 1 cm) densities were noted in the region, consistent with iliac lymph nodes. Multiple small 1-cm parenchymal nodules were found in the lung bases bilaterally, read as most consistent with metastatic disease and confirming the lesions seen on the chest radiograph. No abnormalities of the liver were noted. In addition, an incidental thrombosis of her left common femoral vein was present.

With lung metastases, the tumor was classified as stage III anorectal melanoma.[2] Given the patient's debilitated state and poor life expectancy, abdominoperineal resection was not recommended. Radiotherapy was instituted, with the intent of decreasing the tumor size and bleeding from the tumor. The patient received 30 Gy (10 treatments of 3 Gy per day) to the pelvis with a cone-down boost of 42 Gy to the tumor site. The tumor flattened and decreased in size (to 6 cm × 3 cm, not shown) and ceased bleeding. She died of multiple brain metastases three months after her presentation.

Discussion

Anorectal melanoma is an uncommon malignant neoplasm, representing about 1% of colorectal cancers and less than 2% of all melanomas.[3-7] The typical presentation of these tumors is rectal bleeding, often misdiagnosed as hemorrhoids.[4-8] Patients may have rectal pain, obstipation, or a protruding mass.[9,10] This tumor typically arises from melanocytic cells of the anal mucosa.[9,10] Histologic examination reveals spindle or nevoid cells (or both) forming a pattern reminiscent of acral lentiginous melanomas.[9]

The overall prognosis for patients with anorectal melanoma is poor, with five-year survival rates generally less than 10% despite surgical resection.[4,5,9,11] The tumor behaves aggressively, often invading the lamina propria and muscular layers and may invade proximally into the rectal submucosa. These melanomas often form bulky tumors that protrude into the anal canal or rectum as polypoid masses.[5,6,9] The combination of the rich vascularity of the rectal mucosa and the heightened local aggressiveness of these tumors may perhaps lead to earlier metastasis.[6,10] Thus, the combination of biologic aggressiveness and missed or delayed diagnoses contribute to the poor prognosis.[5,8]

The depth of invasion of the tumor has been implicated as the most important prognostic factor, likely related to the factors mentioned earlier.[9] Thus, emphasis should be placed on early diagnosis of these tumors. Indeed, some have suggested that anorectal melanoma should be included in the differential diagnosis of all

Figure 1.—A pigmented mass is shown arising from the right lateral aspect of the anus.

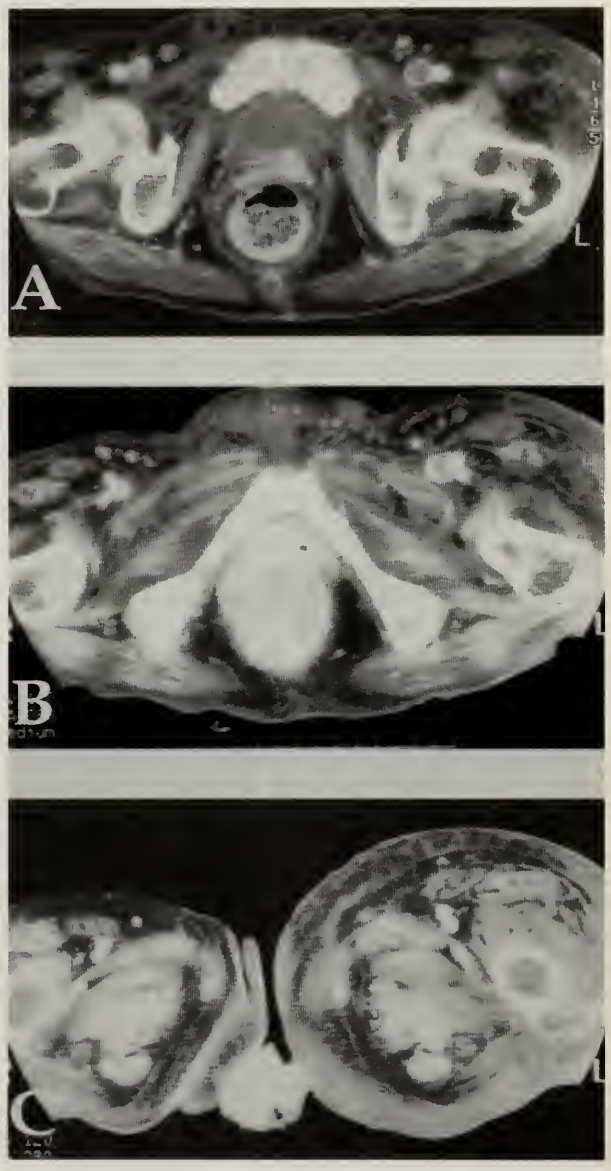

Figure 2.—Computed tomographic scans of the pelvis show craniocaudal and anteroposterior extension of the mass and inguinal lymphadenopathy (A-C). Thrombosis of the left common femoral vein is also noted (A).

between the ages of 45 and 80 who present with rectal bleeding.[6]

Abdominoperineal resection has been the mainstay of the treatment of these tumors.[3] Although this operation results in fewer local recurrences than simple local excision, several studies have failed to show increased survival.[6,7,9,11-13] More recently, anecdotal reports of the response to adjuvant chemotherapy, immunotherapy, or both have appeared.[8,14] Controlled prospective trials to demonstrate the efficacy of such treatment have yet to be done. Radiotherapy has rarely been used palliatively for the treatment of anorectal melanomas.[9,15] Its efficacy in palliating mucosal melanomas of the vagina and rectal region has been reported.[15] Patients with anorectal melanoma had transient benefit, suggesting that irradiation be considered as an alternative to radical surgical therapy in patients with advanced disease.

In summary, anorectal melanoma is an unusual cancer that often presents late in its course. Abdominoperineal resection has not been shown to increase survival in these patients compared with local excision. In advanced cases, such as the one presented here, local excision may not be feasible without substantial morbidity, and more aggressive surgical therapy (such as abdominoperineal resection) is not warranted in the presence of metastatic disease. In light of the short life expectancy of this patient and the limited benefit of surgical therapy, radiotherapy was used as a palliative measure. The approach to patients with advanced anorectal melanoma must include consideration of the patients' quality of life during what are most likely to be their last months. Indeed, some have argued that the therapeutic approach in these patients be aimed primarily at improving the quality of life rather than the minimal increase in survival that a radical surgical procedure affords.[11] Novel approaches to the treatment of all malignant melanomas are being developed. Many melanoma patients mount both humoral and cellular responses against their tumors; this has stimulated research on manipulation of the immune system to target these tumors.[16] The use of monoclonal antibodies, tumor vaccines, adoptive immunotherapy, and gene therapy aimed at increasing the immunogenicity of these tumors is being studied.[16-18] They may provide hope for the future, but until new treatments are developed that are demonstrably efficacious, the therapy for many patients with this disease will be palliative.

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REFERENCES

1. Moore WD: Recurrent melanosis of the rectum after previous removal from the verge of the anus in a man aged sixty-five. Lancet 1857; 1:290-294

2. Balch CM, Houghton AL, Milton GW, Soong S, Sober AJ: Cutaneous Melanoma. Philadelphia, Pa, JB Lippincott, 1992

3. Thomson JPS, Akwari OE: Disorders of the anal canal, *In* Textbook of Surgery: The Biological Basis of Surgical Practice. Philadelphia, Pa, WB Saunders, 1991, pp 958-972

4. Abbas JS, Karakousis CP, Holyoke ED: Anorectal melanoma: Clinical features, recurrence and patient survival. Int Surg 1980; 65:423-426

5. Angerås U, Jönsson N, Jönsson PE: Primary anorectal malignant melanoma. J Surg Oncol 1983; 22:261-264

6. Slingluff CL Jr, Vollmer RT, Seigler HF: Anorectal melanoma: Clinical characteristics and results of surgical management in twenty-four patients. Surgery 1990; 107:1-9

7. Slingluff CL Jr, Seigler HF: Anorectal melanoma: Clinical characteristics and the role of abdominoperineal resection. Ann Plast Surg 1992; 28:85-88

8. Miyahara M, Saito T, Sato K, et al: Primary anorectal malignant melanoma. Surg Today 1992; 22:171-175

9. Wanebo HJ, Woodruff JM, Farr GH, Quan SH: Anorectal melanoma. Cancer 1981; 47:1891-1900

10. Braastad FW, Dockerty MB, Dixon CF: Melano-epithelioma of the anus and rectum. Surgery 1949; 25:82-85

11. Siegal B, Cohen D, Jacob ET: Surgical treatment of anorectal melanomas. Am J Surg 1983; 146:336-338

12. Ross M, Pezzi C, Pezzi T, Meurer D, Hickey R, Balch C: Patterns of failure in anorectal melanoma—A guide to surgical therapy. Arch Surg 1990; 125:313-316

13. Ward MW, Romano G, Nicholls RJ: The surgical treatment of anorectal malignant melanoma. Br J Surg 1986; 73:68-69

14. Freedman LS: Malignant melanoma of the anorectal region: Two cases of prolonged survival. Br J Surg 1984; 71:164-165

15. Harwood AR, Cummings BJ: Radiotherapy for mucosal melanomas. Int J Radiat Oncol Biol Phys 1982; 8:1121-1126

16. Crowley NJ, Seigler HF: Possibilities of immunotherapy and gene therapy for malignant melanoma. Semin Surg Oncol 1993; 9:273-278

17. Slingluff CL Jr, Seigler HF: Prospects for cellular immunotherapy for metastatic melanoma. Ann Plast Surg 1992; 28:110-113

18. Slingluff CL Jr, Seigler HF: Immunotherapy for malignant melanoma with a tumor cell vaccine. Ann Plast Surg 1992; 28:104-107

Editorial

Pulsus Irregularis Perpetus—100 Years of Progress, But Many Issues Still Unresolved

It has now been 100 years since James Mackenzie, a general practitioner in England, recorded a jugular venous and carotid arterial pulse tracing in a patient with "pulsus irregularis perpetus," also referred to as "delerium cordis," documenting the irregularity of the pulse and the absence of any evidence of atrial contraction, which he mistakenly attributed to paralysis of the atria.[1] Three years later, Arthur Cushney, a Scottish physiologist working at the University of Michigan, noted the similarity between these types of pulse tracings and those of open-chested dogs in physiology laboratories recorded "when the auricle is undergoing fibrillary contractions."[1] Cushney, along with other investigators, correctly concluded that atrial fibrillation was the cause of the clinical syndrome of pulsus irregularis perpetus.

In the decades that followed, the principles of clinical management of this common and troublesome arrhythmia were gradually developed, some of which are still valid today and others of which have undergone drastic revision as new data have become available. An example of a clinical practice that has stood the test of time is the use of digitalis to control the ventricular rate. On the other hand, our enthusiasm for the use of agents such as quinidine, which for many years was a mainstay of therapy for atrial fibrillation, has been greatly dampened by the realization that these drugs may suppress the fibrillation but kill the patient.[2,3] The maintenance of sinus rhythm is a worthy goal, but certainly not one worth dying for.

The current state of the art in the management of atrial fibrillation is described by Peter J. Kudenchuk, MD, elsewhere in this issue of The Western Journal of Medicine.[4] This excellent review article summarizes all of the key issues relevant to the clinical management of atrial fibrillation, some of which are as yet unresolved. The hope is that an update of this article will soon be necessary to describe the results and implications of ongoing or planned studies aimed at resolving the following issues:

- Is it better (or safer) to try to suppress atrial fibrillation or to control the ventricular rate and provide adequate prophylaxis against thromboembolic complications?
- Does the maintenance of sinus rhythm eliminate the risk of thromboembolic complications in patients with atrial fibrillation?
- What is the mechanism of the atrial "stunning" that occurs with the conversion of atrial fibrillation, and can it be prevented?
- Is catheter ablation of atrioventricular conduction and the insertion of a permanent pacemaker a more efficacious or cost-effective form of management than pharmacologic therapy for atrial fibrillation?
- How deleterious to cardiac function is the irregularity that accompanies atrial fibrillation?
- Might catheter ablation and pacing to restore regularity be of value in patients with cardiomyopathy and atrial fibrillation?
- Why does "atrial fibrillation beget atrial fibrillation," and can this phenomenon be prevented?
- What is the role of an implanted atrial defibrillator in the management of this arrhythmia?
- Can atrial fibrillation be effectively and safely eliminated using catheter ablation techniques?

In the past 100 years, our understanding of atrial fibrillation has grown in leaps and bounds, evolving from the initial recognition of this arrhythmia in Mackenzie's pulse tracings to a detailed description of the activation patterns of different types of atrial fibrillation based on the elegant intraoperative mapping studies of Konings and co-workers.[5] Although we have learned much about pulsus irregularis perpetus, it is clear that there is also much yet to be learned. The good news is that this fascinating arrhythmia has now drawn the attention of a large number of investigators, and it is likely that we will not have to wait another 100 years for most of the remaining important issues to be resolved.

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REFERENCES

1. Cushney A, quoted in Fye WB: Disorders of the heartbeat: A historical overview from antiquity to the mid-20th century. Am J Cardiol 1993; 72: 1055-1070

2. Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC: Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: A meta-analysis of randomized controlled trials. Circulation 1990; 82:1106-1116

3. Flaker GC, Blackshear JL, McBride R, Kronmal RA, Halperin JL, Hart RG: Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. J Am Coll Cardiol 1992; 20:527-532

4. Kudenchuk PJ: Atrial fibrillation—Pearls and perils of management. West J Med 1996; 164:425-434

5. Konings KT, Kirchhof CJ, Smeets JR, Wellens HJ, Penn OC, Allessie MA: High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994; 89:1665-1680

Commentary

Evolution of Form and Circumstance in Medical Oaths

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Few deny the importance of medical oaths. They are used in a solemn ceremony where, before peers and public, the medical graduate voluntarily witnesses to service to others by lifelong, self-imposed moral principles. By examining the use and form of medical oaths sworn in North American medical schools, patterns emerge that indicate evolving moral aspirations of the medical profession. In this article we address the content and circumstances of medical oaths in 1969, 1979, 1989, and 1994 and compare them with the earliest survey of 1959. We also look at changes by faculty in 1969, 1979, and 1989.

Method

The pioneering study of the use of medical oaths was conducted 35 years ago by sociologists Irish and McMurry.[1] They focused on possible geographic implications in oath taking in North America, treating United States and Canadian medical schools as separate cohorts. As will be seen, differences between the two regions have persisted over time.

In this survey, which follows Irish and McMurry's method, medical school deans listed in the medical education edition of the *Journal of the American Medical Association* (1988; 260:1131-1135) and the *Canadian Medical Directory*[2] were contacted by mail. The survey included a letter to each dean explaining the data sought through explicit questions as well as examples of the modernized form of the Hippocratic Oath as used by the Ohio State University School of Medicine (Columbus) and the Oath of Geneva. Requests for responses in 1969 were repeated until close to a 100% US response was obtained. In 1979, 1989, and 1994, no more than two requests for responses were made. As Table 1 shows, response rates for 1979, 1989, and 1994 were above 90%, which compares well with a rate of 99% in 1959 and a 100% US response in 1969.[3] As a further indication of interest, many deans requested a report of the final findings.

Many variations in the medical oaths are reported. Working from respondents' descriptions, frequently accompanied by a copy of the actual oath used at the medical school, medical oaths were classified into categories by the following rationale: If sworn by Apollo and the ancient gods, it was "Hippocratic" (Figure 1). If it was similar in nature to the modified Hippocratic Oath as used by Ohio State University School of Medicine in 1957 (Figure 2), it was classified as "modified." If it was in the form of the Oath of Geneva, secular promises made freely and upon one's honor, it was classified as the "Geneva Oath" (Figure 3). The oaths classified as "prayer of Maimonides" included those named as such and others that contained a reference to the "father of mercy." The oath was classified as "covenant" if it involved an active dialogue with the audience for agreement to be kept by both the oath taker and oath giver. If the oath did not fall into any of these categories, it was classified as "other." When a medical school reported administering a medical oath but did not specify either its form or content, the oath was classified as "unknown."

Results

Table 2 reveals a 25-year use of medical oaths by more than 90% of US reporting medical schools, whereas in 1959 a little less than 73% of reporting schools used medical oaths. Consequently, a substantial majority of US medical graduates currently practicing in the United States at some time in their careers have sworn a medical oath. This level of use is not true for Canadian medical schools, where the percentage reporting medical oath use has never exceeded 75% and has been as low as 50%.

Form of Oath Used

Table 3 reflects differing definitions of categories of medical oaths over time. The category of "other" reported in the 1959 study delineates Hippocratic oaths or the Ohio State versions with slight changes in wording. As minor editorial changes are no longer considered important, all slightly changed Hippocratic oaths are now included under the category "modified." Canadian schools never reported using the classical Hippocratic Oath. If a school used more than one oath, only one has

(Crawshaw R, Link C: Evolution of form and circumstance in medical oaths. West J Med 1996; 164:452-456)

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Hippocratic Oath

I will look upon him who shall have taught me this Art even as one of my parents. I will share my substance with him, and I will supply his necessities, if he be in need. I will regard his offspring even as my own brethren, and I will teach them this Art, if they would learn it, without fee or covenant. I will impart this Art by precept, by lecture, and by every mode of teaching, not only to my own sons but the sons of him who has taught me, and to disciples bound by covenant and oath, according to the Law of Medicine.

The regimen I adopt shall be for the benefit of my patients according to my ability and judgment, and not for their hurt or for any wrong. I will give no deadly drug to any, though it be asked of me, nor will I counsel such, and especially I will not aid a woman to procure abortion. Whatsoever house I enter, there will I go for the benefit of the sick, refraining from all wrongdoing or corruption, and especially from any act of seduction, of male or female, of bond or free. Whatsoever things I see or hear concerning the life of men, in my attendance on the sick or even apart therefrom, which ought not to be noised abroad, I will keep silence thereon, counting such things to be sacred secrets.

Figure 1.—This Hippocratic Oath is taken from the "Hippocratic Collection" (from the *Encyclopaedia Britannica*, Vol 15, Chicago, Illinois, 1947, p 198).

been included in Table 3, with preference in tabulating given to the oath in most general use, Hippocratic, modified, or Geneva.

The versions of oaths used in the United States show a decrease in the classical Hippocratic Oath from a high of 30.8% in 1969 to 27.4% in 1989, followed by a slight increase in 1994 to 36%. Swearing by the classical Hippocratic Oath's pagan god Apollo or referring to "the cutting for stones" has become uncommon over the past 35 years, whereas the use of a modified Hippocratic Oath has increased from 33.3% to 59.9%. Some form of the Hippocratic Oath is the most common oath in use.

The Geneva Oath remains unaltered except for relatively minor editorial changes, such as adding "sisters" to "brothers." Its use varied from 17.7% in 1959 to 34.3% in 1979, falling off to 30.0% in 1989 and 24.1% in 1994.

The use of alternative medical oaths (designated as "other") follows an erratic trend. Though neither an oath nor a bequest of antiquity, the Prayer of Maimonides, written about 1886, is sometimes used in conjunction with medical oaths. The LaSagna Oath, or Covenant, and the Clouser Covenant appear in the surveys after 1979. In 1994 three French Canadian medical schools reported using a professional oath of unknown derivation required and administered by the president of the provincial professional corporation, the equivalent of a US state board of medical licensure. As some US schools encourage students to choose the oath they wish to swear, idiosyncratic oaths written by faculty members or students appear sparingly but increasingly throughout the surveys. The literature cites a few instances of medical oaths offered by active practitioners for use without public witnessing.[4]

Content

Over the 35-year span of the surveys, reported medical oaths uniformly dealt with personal commitment, the primary concern for patients' well-being, the need for confidentiality, and abstention from wrongdoing. The ancient expression for academic responsibility to teachers appears less and less. By 1979 a number of particular concerns appear, including statements concerning gender, the environment, atomic warfare, and the sanctity of life.

An interesting development in content surfaces in 1989 with the use of a covenant, rather than a personal oath. The covenant represents an ancient Muslim medical tradition that was not incorporated into medical practice during the Middle Ages when European universities regained contact with the Hippocratic corpus preserved by Islam.[5] Today the covenant appears in graduation ceremonies as a solemn dialogue between the graduates and the audience present. Contemporary principles of professional responsibility are addressed in the covenant through a series of declarations by the graduates, followed by responses from the faculty and the audience. The covenant concludes with a mutual witnessing to shared dedication.

Oath of Hippocrates

I do solemnly swear, by whatever I hold most sacred, that I will be loyal to the profession of medicine and just and generous to its members.

That I will lead my life and practice my Art in uprightness and honor.

That into whatsoever home I shall enter, it shall be for the good of the sick and the well to the utmost of my power and that I will hold myself aloof from wrong and from corruption and from the tempting of others to vice.

That I will exercise my Art solely for the cure of my patients and the prevention of disease and will give no drugs and perform no operation for a criminal purpose and far less suggest such a thing.

That whatsoever I shall see or hear of the lives of men which is not fitting to be spoken, I will keep inviolably secret. . . .

These things I do promise, and in proportion as I am faithful to this oath, my happiness and good repute be ever mine, the opposite if I shall be forsworn.

Figure 2.—This oath, sworn by what is held most sacred and not by pagan gods, was used by the Ohio State University School of Medicine, Columbus, in 1957.

Declaration of Geneva

A pledge suggested as a dedication of the physician to his profession of service

At the time of being admitted as a Member of the Medical Profession:

I solemnly pledge myself to consecrate my life to the service of humanity.

I will give to my teachers the respect and gratitude which is their due;

I will practice my profession with conscience and dignity;

The health of my patient will be my first consideration;

I will respect the secrets which are confided in me;

I will maintain by all the means in my power, the honor and the noble traditions of the medical profession;

My colleagues will be my brothers and sisters;

I will not permit considerations of religion, nationality, race, party politics, or social standing to intervene between my duty and my patient;

I will maintain the utmost respect for human life, from the time of conception; even under threat, I will not use my medical knowledge contrary to the laws of humanity.

I make these promises solemnly, freely, and upon my honor.

Figure 3.—The Declaration of Geneva was adopted by the General Assembly of the World Medical Association in Geneva, Switzerland, in 1948 and was suggested as a replacement for the traditional Hippocratic Oath. It is used by the medical fraternity Alpha Omega Alpha at inauguration ceremonies.

Consideration of Change by Faculty

Over the years respondents have volunteered that although the faculty had not initiated changes, students had. Information volunteered along with the 1994 survey reveals that the graduating classes in at least 18 medical schools determined for themselves the form and place for their oath swearing.

Circumstance of Swearing of an Oath

Commencement is reported as the most common time and place for oath taking. By 1994, however, increasing originality and flexibility appeared in both the timing and sites of oath taking. Although the precise details were not provided, it can be reported that a few schools administer a medical oath to their freshman class, and some await completion of postgraduate training. Most reserved a discrete time before their university's convocation for the swearing of an oath together with a hooding or honors ceremony. One medical school invites alumni present to join in reaffirming their medical oath. In another, the ceremony is designated "shingles night" when, following oath taking, each graduate is presented with a shingle bearing the student's name and intended to adorn his or her new office.

Discussion

The sustained use of medical oaths by US medical schools appears to be more than the inertia of social custom, as it is accompanied by a focused evaluation of their contents. Although the prime goal in oath taking remains witnessing to personal moral commitment in caring for patients, increased consideration of religious and governmental issues that impinge on professional behavior reflects the concern of students and faculty in meeting new challenges to the moral nature of medical education and the consequent practice of medicine.

Medical oaths have had to achieve an elemental balance with secular and religious powers. Although Apollo has receded as the authority for medical oaths, religious prayers are currently said during oath-taking ceremonies in 11 US and Canadian medical schools. In seven schools, graduates swear no oath but repeat Maimonides' prayer. One medical school uses an original Christian medical oath.

The Quebec Professional Corporation, which corresponds to a state board of medical license in the United States, reports a new dimension between medical oath swearing and government in operation since 1979 (oral communication, December 1994). The corporation requires MD graduates to complete an additional two years of postgraduate training in family practice before swearing the corporation's medical oath, following which a license is granted to practice medicine. Five medical schools report that the sponsoring authority for swearing shifted from academic faculties to the provincial government. The Quebec Oath, of unknown derivation, is administered by the corporation's president before a table on which sit a Catholic bible, a Protestant bible, a Jewish torah, and the Koran.

For those seeking a license to practice in Quebec, the government's required oath blurs the boundary between

TABLE 1.—*Response Rate for Surveys**

Country	*1959*	*1969*	*1979*	*1989*	*1994*
USA					
Schools, No.	85	86	114	126	125
Response, %	98.8	98.8	97.4	95.2	92.8
Canada					
Schools, No.	12	12	16	16	16
Response, %	100.0	91.7	93.8	100.0	93.8

*From the 1959 data from Irish and McMurry[1] and 1969-1994 data from surveys administered by Ralph Crawshaw.

TABLE 2.—*Use of Medical Oath, %**

Country	*1959*	*1969*	*1979*	*1989*	*1994*
USA					
Yes	72.9	90.7	92.1	93.7	92.8
No	25.9	8.1	5.3	1.6	0.0
No response	1.2	1.2	2.6	4.8	7.2
Canada					
Yes	58.3	50.0	75.0	75.0	56.2
No	41.7	41.7	18.8	25.0	37.5
No response	0.0	8.3	6.2	0.0	6.2

*From the 1959 data from Irish and McMurry[1] and 1969-1994 data from surveys administered by Ralph Crawshaw.

a medical oath and a loyalty oath. Quebec applicants are afforded no personal choice in witnessing. Although this obligatory oath verges on coerced civic witnessing, to date no Quebec physician is reported to have protested; rather, Quebec authorities anticipate a similar requirement to spread to the other Canadian provinces.

The abrupt increase in the use of the Geneva Oath in 1979, followed by a later decline, may represent its use as an alternative to the classical Hippocratic Oath that in the 1960s was considered anachronistic. Revisions in the Hippocratic Oath after 1979 rendered it more acceptable to schools that had switched to the Geneva Oath.

In place of a medical oath, the Covenant, with its original content and unique delivery, offers a structured dialogue among the graduates, the faculty, and the assembled public.[6] The individual declaration of the graduate with its implied one-to-one relationship with the patient has been amplified into a communitarian bond. Participants forthrightly acknowledge a mutual relationship through shared responsibilities expressing an enhanced sense of community. This evolution of oath taking indicates a growing recognition of social interdependence among physician, patient, and community, including an appreciation of population-based medicine.

Roger Bulger, MD, President of the Association of Academic Health Centers, reports that his organization circulated a "health professional covenant" for nursing, social work, and psychology graduates as well as medical graduates (oral communication, February 1995). In 1995 the "patient-physician covenant" appeared as a response to excessive commercialization of medical practice. It is now under consideration by medical faculties and many medical associations in the United States for endorsement and public witnessing.[7]

Although not directly related to taking a medical oath, another sacred ceremony, a unique ritual for delineating physicians' respectful dedication, was met with in the course of the study. The ceremony is conducted at the graveside of cadavers used in the study of anatomy. Medical students, faculty, and family members of the dead are welcome to participate, and it is not unusual for 100 family members to attend the graveside ceremony. Approximately half of the ashes of each body are returned to the family. The remaining ashes are contained in a biodegradable carton inscribed with the name of the donor and placed in a common grave, along with a single carnation. A simple, nondenominational religious service is conducted, earth strewn over the

TABLE 3.—*Form of Oath Used, %*†*

Country	*1959*	*1969*	*1979*	*1989*	*1994*
USA					
Hippocratic	11.3	30.8	7.6	3.4	5.2
Modified	22.6	33.3	40.0	55.9	56.9
Geneva	17.7	26.9	34.3	30.0	24.1
Covenant	--	0.0	0.0	0.8	0.0
Prayer of Maimonides	--	0.0	5.7	3.4	3.4
Other	46.8	7.7	9.5	7.6	10.3
Unknown	1.6	1.3	2.9	0.0	0.0
Canada					
Hippocratic	0.0	0.0	0.0	0.0	0.0
Modified	0.0	16.7	25.0	16.7	33.4
Geneva	14.3	16.7	16.7	16.7	22.2
Covenant	--	0.0	0.0	0.0	0.0
Prayer of Maimonides	--	0.0	0.0	0.0	0.0
Other	85.7	66.7	58.3	66.7	44.4
Unknown	0.0	0.0	0.0	0.0	0.0

*From the 1959 data from Irish and McMurry[1] and 1969-1994 data from surveys administered by Ralph Crawshaw.
†See text for description of classification of oaths.

remains, and the grave closed. The ceremony is completed with a grave marker without names but with the simple inscription, "The Ultimate Gift" (Jack Davies, MD, Professor Emeritus of Anatomy, Vanderbilt University School of Medicine, Nashville, Tennessee, oral communication, April 1988).

Future surveys should determine who, if anyone, among faculty, students, and the public are actively considering changes. This should assist in identifying those seeking change as well as possible motives.

REFERENCES

1. Irish DF, McMurry M: Professional oaths and American medical colleges. J Chronic Dis 1965; 15:275-289
2. Canadian Medical Directory. Don Mills, Ontario, Southampton Magazine and Information Group in association with the Canadian Medical Association, 1988, pp 37-53
3. Crawshaw R: Contemporary use of medical oaths. J Chronic Dis 1970; 23:144-150
4. Crawshaw R: Physician's oath for self-insight. Ann Intern Med 1979; 91:648
5. Jones WHS: The Doctor's Oath—An Essay in the History of Medicine. Cambridge, England, Cambridge Press, 1924, p 30
6. Clouser KD: The covenant. Ann Intern Med 1989; 103:941-943
7. Crawshaw R, Rogers D, Pellegrino E, et al: Patient-physician covenant. JAMA 1995; 273:1553

Lessons From the Practice

Terry and the Fly

KIM MARIE THORBURN, MD, *Honolulu, Hawaii*

Terry's nosebleeds were frequent and uncontrollable. To see him, I had to pass through three guarded, steel-grated gates in the 50-year-old hospital at San Quentin (California) Prison, into the protective custody area. Terry could not circulate among the general prison population. He spent his prison days in isolation, lest he be killed by another inmate.

I did my best to reach out to this sullen and uncommunicative young man. According to prison medicine etiquette, I never asked about his crime nor much about the reason for protective custody. It was not until later, as our physician-patient relationship unfolded, that he revealed his fear of enemies among the convicts. I heard that he was a dropout from a Mexican prison gang that admits a few non-Hispanic whites like Terry.

Physicians in the past had tried many remedies to control Terry's nosebleeds. Calling on an otolaryngologic consultant, I, too, sought a means to stop the severe epistaxis. We looked for a surgically treatable lesion with scans and arteriography, but repeated examination could not locate the bleeding site. Invasive treatments, including cautery and internal carotid ligation, led to further complications, and the bleeding would always begin again.

I met "the Fly" about the same time I met Terry. The Fly was also a bleeder, locked in protective custody, and a dropout from another Mexican prison gang. He had been behind bars for many years. We often discussed his mother, whom he adored. After he betrayed his gang brothers, she was his only contact with the outside world. How the Fly despaired that he was not a good son!

The Fly escaped his sorrows in prison-made wine, "pruno," brewed from anything that fermented. He was an alcoholic. His usual presentation was that of a mean, nasty drunk carried in by guards and kicking and screaming with blood dripping from his mouth.

My examination of this unpleasant inebriate was cursory to avoid a bolus of spittle or a blow from a flailing extremity. Someday I intended to work the Fly up for hematemesis, but thought that the blood dribbling from his mouth was peculiar for that symptom.

Neither Terry nor the Fly bled when they were residing in the prison hospital. I admitted each frequently, always over their initial raucous objections. Then they would settle comfortably for my care and concern. I tried to balance medical interventions yet avoid escalating their desperate need for attention.

After a few months, I turned to conservative measures to control Terry's epistaxis, but these were no more successful than invasive treatments. I suspected him of nose-picking. I clipped his fingernails. Nasal packings fell out. Yet, his hemoglobin continued to fall so low that he would stagger when he stood up. I finally settled into a pattern of admitting him for a transfusion when his hemoglobin dropped to 50 or 60 grams per liter (5 or 6 grams per dl). Sometimes it would be a month or more between admissions; sometimes only a few days.

Terry was fascinated by the life-sustaining blood transfusions, but they caused me grave concern. He developed febrile reactions and hepatitis, complications of the nearly 100 units he received.

Despite my professional efforts, it was obvious that any maternal role was important to Terry. I knew much about Terry by then—his happy early childhood in a middle-class family, his success in school, his fury at the divorce of his parents, and the sense of desertion by both. I liked Terry, but I just wished he would stop bleeding.

I struggled more with my feelings about the Fly. His episodes were never critical. The alcoholic binges were a device to see me, a mother substitute. Finally, I gave the Fly an ultimatum: I would be his physician but not when he was drunk. I promised regular appointments. This worked well for a while, but then one day the Fly was carried in—kicking, biting, and spitting—with prison guards restraining each extremity. He was drunk and nasty with bright red blood dripping from his mouth. He softened a bit when I arrived, but I stuck to my warning and called another physician.

The Fly was not admitted during this relapse. The other physician received an eyeful of bloody spittle. More drunk than sick, the Fly was discharged to sleep off the condition in his cell. The guards, however, decided that further investigation was in order. Back in the Fly's cell, foregoing the delicacy of medical examination, they looked in his mouth and discovered a razor blade. After that, the Fly never bled per orum again.

(Thorburn KM: Terry and the Fly. West J Med 1996; 164:457-458)

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I saw the Fly for relapses of more blatant self-mutilation, but our relationship grew more episodic, in part because I felt a sense of failure in caring for this man. A few months later, after I left San Quentin, the Fly was found dead, hanging in his cell.

Terry was eventually paroled. He joined his reunited parents, fulfilling his lost childhood dream. Despite his outward pleasure, his need for transfusions continued. The only time I heard about Terry after he left prison was from an otolaryngologist who was considering sewing his nostrils closed.

"Some psychiatric conditions are terminal," instructed a psychiatrist when I had sought advice on caring for these men. She said it sympathetically, but the counsel seemed too cold and hardened. Remembering her words now provides some solace. I thought that if I could not cure, I could at least care. But even caring was not enough to ease the suffering of Terry or the Fly.

* * *

Lessons From the Practice

The Toxic Intern Has CEX

FRANCES SPECTOR, MD, *San Jose, California*

Dr Spector's right on time. She's having sex today with Dr S." The women working in the clinic are clearly having fun the day of my Clinical Evaluation Exercise (CEX) session. "You're having CEX in room 8." Of course, I join in the banter. We all amuse ourselves for the next few minutes. Then someone discovers that the patient I am to examine and whose case I am to present while observed by the clinic director is nowhere around.

It's a post-call day. I was too busy earlier to think about this, but now I have stage fright. Women's laughter helps. They'll page me when they find the patient.

Mrs C sits in the room, and the attending physician says, "Let's go." He's famous (tells you so himself) for his short attention span: "Yeah, yeah, yeah," the legs crossed, the top foot swinging. Now he's prepared to suffer through an hour, maybe two hours, of my history taking, physical examination, and case presentation.

Dr S enters room 8 first, asking Mrs C's permission for his presence. Tense and tachycardic, I follow him. Nothing will slow me down or distract me from getting the complete history in record time.

"They told me to give you this," she says, and hands me the history form that patients are supposed to fill out. It's completely blank. Nothing will slow me down. I've already read her chart, so I'm not going to waste time.

"I notice you had a breast mass removed recently. Tell me about that."

Half an hour later, we're out of the room. I face my inquisitor.

"A solid job, very complete. But I usually shake hands and introduce myself to a new patient."

(So do I, don't I?)

"And it's better to start by asking why the patient is coming to see you, rather than with your agenda."

(Yes, yes, I know. I think I know that.)

The physician who was in the examining room isn't recognizable anymore. She was just a data gatherer. I go back in to the examination room, sit down, and give Mrs C my card.

"I'm Dr Spector. I just realized I never introduced myself." I offer my hand.

She takes it, saying, "I was wondering who you were." (So was I.)

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Spector F: The toxic intern has CEX. West J Med 1996; 164:458)

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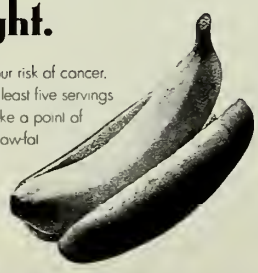

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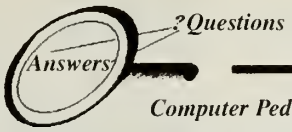

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California Medical Association–PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 21-25, 1997, SF Hilton, San Francisco.

Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 20-22, 1996, Steam Boat Sheraton, Steam Boat Springs.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1996, Sun Valley Inn, Sun Valley, Idaho.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 25-28, 1996, Newport Beach, California; 1997, date and location to be announced.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 9-11, 1996, New Mexico Medical Society Offices, Albuquerque; 1997, date and location to be announced.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 25-28, 1996. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 26-28, 1996. Tacoma Sheraton, Tacoma.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 13-15, 1996, Jackson Lake Lodge, Moran.

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CONTRAINDICATIONS: Known hypersensitivity to nifedipine.

WARNINGS: Excessive Hypotension: Although in most patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients using concomitant beta-blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients who received immediate release capsules together with a beta-blocking agent and who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta-blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction upon starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta-Blocker Withdrawal: When discontinuing a beta-blocker it is important to taper its dose, if possible, rather than stopping abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients (usually while receiving a beta-blocker) have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to these patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General - Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of ADALAT CC is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure (See WARNINGS).

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose-dependent manner with ADALAT CC. The placebo subtracted rate is approximately 8% at 30 mg, 12% at 60 mg and 19% at 90 mg daily. This edema is a localized phenomenon, thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Information for Patients: ADALAT CC is an extended release tablet and should be swallowed whole and taken on an empty stomach. It should not be administered with food. Do not chew, divide or crush tablets.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small increase (<5%) in mean alkaline phosphatase was noted in patients treated with ADALAT CC. This was an isolated finding and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported with nifedipine treatment. In controlled studies, ADALAT CC did not adversely affect serum uric acid, glucose, cholesterol or potassium.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs' test with or without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions: Beta-adrenergic blocking agents: (See WARNINGS).

ADALAT CC was well tolerated when administered in combination with a beta blocker in 187 hypertensive patients in a placebo-controlled clinical trial. However, there have been occasional literature reports suggesting that the combination of nifedipine and beta-adrenergic blocking drugs may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina in patients with cardiovascular disease.

Digitalis: Since there have been isolated reports of patients with elevated digoxin levels, and there is a possible interaction between digoxin and ADALAT CC, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing ADALAT CC to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Quinidine: There have been rare reports of an interaction between quinidine and nifedipine (with a decreased plasma level of quinidine).

Cimetidine: Both the peak plasma level of nifedipine and the AUC may increase in the presence of cimetidine. Ranitidine produces smaller non-significant increases. This effect of cimetidine may be mediated by its known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. In rodents, rabbits and monkeys, nifedipine has been shown to have a variety of embryotoxic, placentotoxic and fetotoxic effects, including stunted fetuses (rats, mice and rabbits), digital anomalies (rats and rabbits), rib deformities (mice), cleft palate (mice), small placentas and underdeveloped chorionic villi (monkeys), embryonic and fetal deaths (rats, mice and rabbits), prolonged pregnancy (rats; not evaluated in other species), and decreased neonatal survival (rats; not evaluated in other species). On a mg/kg or mg/m^2 basis, some of the doses associated with these various effects are higher than the maximum recommended human dose and some are lower, but all are within an order of magnitude of it.

The digital anomalies seen in nifedipine-exposed rabbit pups are strikingly similar to those seen in pups exposed to phenytoin, and these are in turn similar to the phalangeal deformities that are the most common malformation seen in human children with *in utero* exposure to phenytoin.

There are no adequate and well-controlled studies in pregnant women. ADALAT CC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nifedipine is excreted in human milk. Therefore, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE EXPERIENCES: The incidence of adverse events during treatment with ADALAT CC in doses up to 90 mg daily were derived from multi-center placebo-controlled clinical trials in 370 hypertensive patients. Atenolol 50 mg once daily was used concomitantly in 187 of the 370 patients on ADALAT CC and in 64 of the 126 patients on placebo. All adverse events reported during ADALAT CC therapy were tabulated independently of their causal relationship to medication.

The most common adverse event reported with ADALAT® CC was peripheral edema. This was dose related and the frequency was 18% on ADALAT CC 30 mg daily, 22% on ADALAT CC 60 mg daily and 29% on ADALAT CC 90 mg daily versus 10% on placebo.

Other common adverse events reported in the above placebo-controlled trials include: Headache (19%, versus 13% placebo incidence); Flushing/heat sensation (4%, versus 0% placebo incidence); Dizziness (4%, versus 2% placebo incidence); Fatigue/asthenia (4%, versus 4% placebo incidence); Nausea (2%, versus 1% placebo incidence); Constipation (1%, versus 0% placebo incidence).

Where the frequency of adverse events with ADALAT CC and placebo is similar, causal relationship cannot be established.

The following adverse events were reported with an incidence of 3% or less in daily doses up to 90 mg:

Body as a Whole/Systemic: chest pain, leg pain **Central Nervous System:** paresthesia, vertigo **Dermatologic:** rash **Gastrointestinal:** constipation **Musculoskeletal:** leg cramps **Respiratory:** epistaxis, rhinitis **Urogenital:** impotence, urinary frequency

Other adverse events reported with an incidence of less than 1.0% were:

Body as a Whole/Systemic: cellulitis, chills, facial edema, neck pain, pelvic pain, pain **Cardiovascular:** atrial fibrillation, bradycardia, cardiac arrest, extrasystole, hypotension, palpitations, phlebitis, postural hypotension, tachycardia, cutaneous angiectasis **Central Nervous System:** anxiety, confusion, decreased libido, depression, hypertonia, insomnia, somnolence **Dermatologic:** pruritus, sweating **Gastrointestinal:** abdominal pain, diarrhea, dry mouth, dyspepsia, esophagitis, flatulence, gastrointestinal hemorrhage, vomiting **Hematologic:** lymphadenopathy **Metabolic:** gout, weight loss **Musculoskeletal:** arthralgia, arthritis, myalgia **Respiratory:** dyspnea, increased cough, rales, pharyngitis **Special Senses:** abnormal vision, amblyopia, conjunctivitis, diplopia, tinnitus **Urogenital/Reproductive:** kidney calculus, nocturia, breast engorgement

The following adverse events have been reported rarely in patients given nifedipine in other formulations: allergenic hepatitis, alopecia, anemia, arthritis with ANA (+), depression, erythromelalgia, exfoliative dermatitis, fever, gingival hyperplasia, gynecomastia, leukopenia, mood changes, muscle cramps, nervousness, paranoid syndrome, purpura, shakiness, sleep disturbances, syncope, taste perversion, thrombocytopenia, transient blindness at the peak plasma level, tremor and urticaria.

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Please see brief summary of Prescribing Information on following page.

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† For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect β-lactamase–producing pathogens.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxycillin/clavulanic acid: a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993;5(2):67-93. **2.** *Clinical Efficacy Update I-III*, 1995, SmithKline Beecham Pharmaceuticals.

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***AUGMENTIN*® amoxicillin/clavulanate potassium**
BRIEF SUMMARY. FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.
INDICATIONS AND USAGE: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below
Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Otitis Media* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Sinusitis* caused by β-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*. *Skin* and *Skin Structure Infections* caused by β-lactamase-producing strains of *Staphylococcus aureus, Escherichia coli*, and *Klebsiella* spp. *Urinary Tract Infections* caused by β-lactamase-producing strains of *E. coli, Klebsiella* spp. and *Enterobacter* spp. While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic. Because amoxicillin has greater *in vitro* activity against *Streptococcus pneumoniae* than does ampicillin or penicillin, the majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and *Augmentin*. (See Microbiology subsection.)
Bacteriological studies to determine the causative organisms and their susceptibility to *Augmentin* should be performed together with any indicated surgical procedures. Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once results are known, adjust therapy, if appropriate.
CONTRAINDICATIONS: Patients with a history of allergic reactions to any penicillin, or patients with a history of *Augmentin*-associated cholestatic jaundice/hepatic dysfunction.
WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH *AUGMENTIN*, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.** Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis." After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis. Use *Augmentin* cautiously in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with *Augmentin* use is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
PRECAUTIONS: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.
Drug/Laboratory Test Interactions: Oral administration of *Augmentin* will result in high urine concentrations of amoxicillin. High urine concentrations of ampicillin may result in false-positive reactions when testing for the presence of glucose in urine using Clinitest®, Benedict's Solution or Fehling's Solution. Since this effect may also occur with amoxicillin and therefore *Augmentin*, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used.
Following administration of ampicillin to pregnant women a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with amoxicillin and therefore *Augmentin*.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. **Mutagenesis:** The mutagenic potential of *Augmentin* was investigated *in vitro* with an Ames test, a human lymphocyte cytogenetic assay, a yeast test and a mouse lymphoma forward mutation assay, and *in vivo* with mouse micronucleus tests and a dominant lethal test. All were negative apart from the *in vitro* mouse lymphoma assay where weak activity was found at very high, cytotoxic concentrations.
Impairment of Fertility: *Augmentin* at oral doses of up to 1200 mg/kg/day (5.7 times the maximum human dose, 1480 mg/m²/day, based on body surface area) was found to have no effect on fertility and reproductive performance in rats dosed with a 2:1 ratio formulation of amoxicillin:clavulanate.
Teratogenic effects: Pregnancy (Category B): Reproduction studies performed in pregnant rats and mice given *Augmentin* at oral dosages up to 1200 mg/kg/day, equivalent to 7200 and 4080 mg/m²/day, respectively (4.9 and 2.8 times the maximum human oral dose based on body surface area), revealed no evidence of harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, use this drug during pregnancy only if clearly needed.
Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.
ADVERSE REACTIONS: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were mild and transient, <3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%). The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.
The following adverse reactions have been reported for ampicillin class antibiotics:
Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis, mucocutaneous candidiasis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment. (See WARNINGS.) Skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome) and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis). These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin. (See WARNINGS.) A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported (less than 1 death reported per estimated 4 million prescriptions worldwide). These have generally been cases associated with serious underlying diseases or concomitant medications. Interstitial nephritis and hematuria have been reported rarely. Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*. Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.
DOSAGE AND ADMINISTRATION
Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), 2 *Augmentin* 250 mg tablets are not equivalent to 1 *Augmentin* 500 mg tablet. Therefore, 2 *Augmentin* 250 mg tablets should not be substituted for 1 *Augmentin* 500 mg tablet.
Dosage:
Adults: The usual adult dose is 1 *Augmentin* 500 mg tablet every 12 hours or 1 *Augmentin* 250 mg tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be 1 *Augmentin* 875 mg tablet every 12 hours or 1 *Augmentin* 500 mg tablet every 8 hours.
Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/minute should not receive the 875 mg tablet. Patients with a glomerular filtration rate of 10 to 30 mL/minute should receive 500 mg or 250 mg every 12 hours, depending on the severity of the infection. Patients with a less than 10 mL/minute glomerular filtration rate should receive 500 mg or 250 mg every 24 hours, depending on severity of the infection.
Hemodialysis patients should receive 500 mg or 250 mg every 24 hours. They should receive an additional dose both during and at the end of dialysis.
Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals. (See WARNINGS.)
Pediatric Patients: Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.
Due to the different amoxicillin to clavulanic acid ratios in the *Augmentin* 250 mg tablet (250/125) versus the *Augmentin* 250 mg chewable tablet (250/62.5), the *Augmentin* 250 mg tablet should not be used until the pediatric patient weighs at least 40 kg or more.
Administration: *Augmentin* may be taken without regard to meals, however, absorption of clavulanate potassium is enhanced when *Augmentin* is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, *Augmentin* should be taken at the start of a meal.
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PROTECTING PHYSICIANS

The New CMA

MEDICAL BOARD OF CALIFORNIA

PROTECTING PHYSICIANS

CMA obtained modifications of MBC public disclosure policy to appropriately protect physicians' right to privacy and opposed a licensing fee increase.

- Obtained a preliminary injunction prohibiting MBC from disclosing pre-accusation investigatory information.
- Succeeded in getting MBC to modify its public disclosure policy to address CMA's major concerns.
- Urged the California Supreme Court to review two cases in which the appellate courts had ruled that MBC may access confidential peer review records. The Supreme Court agreed suggesting that the Court is sympathetic to CMA's view that the law bars MBC from reviewing confidential medical staff records.
- When California Physicians were at their breaking point regarding licensing fee increases, CMA single handedly persuaded MBC to retract its proposed $100 fee increase.

PROFESSIONAL LIABILITY

PROTECTING MICRA

The fact that California's malpractice rates are among the lowest in the nation is no accident. Since 1975, when CMA's hard-fought MICRA tort reform was enacted, there has not been a single change. Much credit goes to CMA's attorneys, who monitored all cases involving MICRA and physician's rights in professional liability cases.

- Successfully eliminated, as precedent, a case which would have allowed plaintiffs attorneys to make claims for lost "chance of survival," even when it is more likely than not that physician's alleged negligence had caused harm.

REIMBURSEMENT ASSISTANCE

HELPING PHYSICIANS WITH SPECIFIC PROBLEMS

CMA continued to help many individual members correct payment problems with various carriers and health plans throughout the state. As a result of CMA action, Blue Shield rescinded its request for refunds of payments for claims from about 4,600 physicians. CMA also helped physicians receive refunds from a company that unfairly charged fees to physicians' credit cards.

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SOUTHERN MEDICAL ASSOCIATION

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CME CONFERENCES

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The Cloister, Sea Island, GA
July 22-24, 1996

7th Annual Focus on the Female Patient
Kiawah Island Resort, Kiawah Island, SC
July 22-25, 1996

5th Annual General Surgery Update
The Cloister, Sea Island, GA
July 26-28, 1996

4th Annual Primary Care Update: What's New in Dermatology
Kiawah Island Resort, Kiawah Island, SC
July 26-28, 1996

Sports Medicine & Soccer Symposium
The Parliament House, Birmingham, AL
July 26-28, 1996

Advanced Orthopaedic Imaging
The Cloister, Sea Island, GA
July 29-August 1, 1996

Pain Management in the Office Setting
The Cloister, Sea Island, GA
August 2-4, 1996

Advances in Geriatric Medicine
Lago Mar Resort & Club, Ft. Lauderdale, FL
August 9-11, 1996

Gastroenterology Update for Primary Care
Marriott's Bay Point Resort, Panama City, FL
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Common Clinical & Practice Skills: Use & Interpretation
Ritz-Carlton-Palm Beach, Manalapan, FL
August 23-25, 1996

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Swissotel, Atlanta, GA
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A great success story in 1995, CMA developed California Advantage, Inc. that now has more than 6,500 shareholders and is on track to enter the marketplace on July 1, 1996, with a statewide PPO and EPO offered through the Health Insurance Plan of California.

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As part of CMA's reorganization and its commitment to taking the lead role in shaping the future of health care in California, we are creating a new subsidiary, the Institute for Medical Quality. Initially, it will house CMA's existing quality assurance and accreditation programs. In the future, we plan to develop new accreditation programs relating to quality evaluation of HMOs and integrated health care systems, as well as accreditation of physician offices.

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Brochures and registration forms are available from the contact person or organization sponsoring the program.

August 5-10—**1996 Comprehensive Internal Medicine Board Preparation Course.** Marriott's Camelback Inn, Scottsdale. Mon-Sat. Contact: Beverlee Anderson, (602) 267-5366.

October 7-10—**Visiting Fellowships in MRI.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Thurs. Contact: (800) 848-4920, ext 2575.

October 14-18—**Neuroradiology: Review and Update.** University of Arizona College of Medicine at the Biltmore Advanced Imaging Center, Phoenix. Mon-Fri. Contact: (800) 848-4920, ext 2575.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

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This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

August 2-4—A **Midsummer Night's Wheeze**. American College of Allergy, Asthma and Immunology at La Costa Resort & Spa, Carlsbad. Fri-Sun. 8 hrs, $110-$195. Contact: California Society of Allergy and Clinical Immunology, (714) 828-8022.

CARDIOLOGY

August 8-10—**Critical Care Cardiology**. American College of Cardiology at the Sheraton Palace Hotel, San Francisco. Thurs-Sat. 16.5 hrs. Contact: Registration Secretary, Extramural Programs Dept, ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814. (800) 253-4636.

October 10-12—**Cardiology Update 1996.** American College of Cardiology at Carmel Valley Ranch Resort. Thurs-Sat. 12 hrs. Contact: Registration Secretary, Extramural Programs Dept, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814. (800) 253-4636.

November 22-24—**Coronary Heart Disease Update.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sun. 11 hrs. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421- 3756.

DERMATOLOGY

July 13—**Primary Care Dermatology.** UCD at Cancer Center Auditorium, Sacramento. Sat. 4 hrs, $50-$60. Contact: UCD.

October 5-9—**11th Combined Skin Pathology Course and Workshop in Dermatopathology.** UCSD at San Diego Princess. Sat-Wed. 37 hrs, $600. Contact: UCSD.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

November 2-3—**The Skin From A to Z: Tips on Practical Therapy and Office Techniques.** UCSF. Sat-Sun. Contact: UCSF.

EMERGENCY MEDICINE

October 18-20—**The Comprehensive Review in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hyatt Regency, La Jolla. 20 hrs, $495. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

October 20-23—**Cellular Injury and Brain Edema, 1996.** Foundation for Pediatric and Laser Neurosurgery, Inc, at Hyatt Regency Hotel, San Diego. Sun-Wed. 19 hrs, $350-$400. Contact: Hector E. James, MD, Coordinator, Foundation for Pediatric and Laser Neurosurgery, Inc, 7930 Frost St, Ste 304, San Diego 92123. (619) 560-4791.

October 21-25—**Emergency Medicine Symposium I**. UCSD. Mon-Fri. 32 hrs, $495. Contact: UCSD.

November 11-15—**Emergency Medicine Symposium III**. UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs, $495. Contact: UCSD.

December 16-20—**Emergency Medicine Symposium II**. UCSD. Mon-Fri. 32 hrs, $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

July 8-11—**Family Practice Board Review Course**. UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs, $425-$475. Contact: UCSF.

August 2-4—**Managing Respiratory Diseases.** Medical Education Resources at Tenaya Lodge, Yosemite. Fri-Sun. 11 hrs, $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

August 2-4—**Cardiology for the Primary Care Physician.** Continuing Medical Education Associates at Hotel del Coronado, Coronado. Fri-Sun. 20 hrs, $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 5-7—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, Coronado. Mon-Wed. 20 hrs, $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

August 9-11—**Neurology for the Non-Neurologist.** Medical Education Resources at Doubletree Hotel, Monterey. Fri-Mon. 11 hrs, $375. Contact: Linda Main, Meetings Coordinator, Medical Education Resources, 1500 W Canal Court, Ste 500, Littleton, CO 80120-4569. (800) 421-3756.

August 11-16—**Essentials of Primary Care: A Core Curriculum for Practice in the Managed Care Era.** UCSF at Resort at Squaw Creek, North Lake Tahoe. Sun-Fri. 25 hrs, $645. Contact: UCSF.

October 9-12—**Semiannual Wound Management Workshop: For Primary Care Professionals.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sat. 17 hrs. $475. Contact: UCSD, Edith Bookstein, (619) 454-3212.

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October 21-23—**Neurology and Outpatient Psychiatry in Primary Care.** Continuing Medical Education Associates at Hyatt Regency, San Diego. 20 hrs, $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

INFECTIOUS DISEASE

October 26-November 2—**National Infectious Disease Update Conference.** Santa Rosa Kaiser Permanente Medical Center on the Sun Princess Cruise, Western Caribbean. Sat-Fri. 7 hrs, $50-$100. Contact: Infectious Disease Update/SRO, Kaiser Permanente Medical Center, 401 Bicentennial Way, Santa Rosa 95403-2192.

INTERNAL MEDICINE

September 19-21—**Rheumatology Board Review.** UCSF at Miyako Hotel, San Francisco. Thurs-Sat. 24 hrs. Contact: UCSF.

September 27-October 2—**Internal Medicine 1996—Fall Program.** Continuing Medical Education Associates at Loews Coronado Bay Resort, San Diego. Fri-Wed. $450. Contact: Jacqueline Shiller, PO Box 270469, San Diego 92198. (619) 674-5200.

September 30-October 4—**Texas Internal Medicine Conference.** UCSD at Westgate Hotel, San Diego. Mon-Fri. Contact: UCSD.

October 3-4—**Design and Methods of Clinical Trials.** UCSF at Holiday Inn, Union Square, San Francisco. Thurs-Fri. 12.5 hrs, $285-$375. Contact: UCSF.

NEPHROLOGY

August 2-8—**12th Comprehensive Nephrology Review Course.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Thurs. 50 hrs, $800. Contact: UCLA.

OCCUPATIONAL MEDICINE

August 5-6—**Worker's Compensation Overview/Update.** UC Berkeley at San Francisco Airport Hilton Hotel. Mon-Tues. 12 hrs, $395. Contact: UC Berkeley.

August 8-9—**Ergonomics Case Studies: Techniques for Success.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. 13.5 hrs, $395. Contact: UC Berkeley.

December 5-6—**Occupational Disorders of the Upper Extremities.** UC Berkeley at San Francisco Airport Hilton Hotel. Thurs-Fri. Contact: UC Berkeley.

ONCOLOGY

October 10-12—**20th Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton Harbor Island Hotel, San Diego. Thurs-Sat. 17 hrs, $425-$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, PO Box 28, La Jolla 92038-0028; Ruthanne Crawford, (619) 626-6794.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
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UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

(Continued on Page 476)

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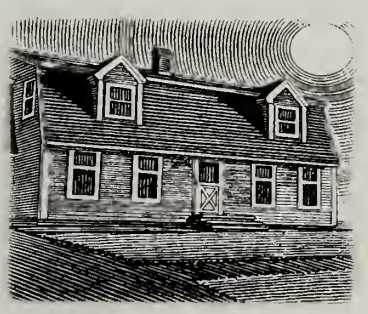

A World Without Trees

The National Arbor Day Foundation

(Continued from Page 475)

October 19—**15th Annual Cancer Memorial Symposium—Winning Strategy Against Cancer.** Victor Valley Community Hospital at Holiday Inn, Victorville. Sat. 8 hrs, $90. Contact: Hi Desert Joint Cancer Program, Alice Williams, CTR Victor Valley Community Hospital, 15248 11th St, Victorville 92392. (619) 245-8691, ext 3432.

OTOLARYNGOLOGY

July 5-7—**Current Concepts in Allergy and Otolaryngology**. Children's Hospital at Le Meridien Hotel, Coronado. Fri-Sun. 14.5 hrs. Contact: Children's Hospital, Continuing Medical Education Office, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

September 14-18—**Temporal Bone Surgical Dissection Courses**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

October 19-23—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

November 7-9— **Otolaryngology Update: 1996.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 18.5 hrs, $425. Contact: UCSF.

November 9-13—**Temporal Bone Surgical Dissection Courses.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079

December 7-11—**Temporal Bone Surgical Dissection Courses**. The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, (213) 483-4431, ext 7079.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

PEDIATRICS

July 11-13—**Adolescent Medicine: A Practical Course for Clinicians**. UCSD at Hilton Beach and Tennis Resort, San Diego. Thurs-Sat. 15 hrs, $350. Contact: UCSD.

July 19-20—**Fourth Annual Pediatric Update**. Stanford University at Lucile Packard Children's Hospital, Palo Alto. Fri-Sat. 14.5 hrs, $275-$300. Contact: Elinor Meyer, CME Coordinator, Lucile Packard Children's Hospital, 725 Welch Rd, Palo Alto 94394. (415) 497-8554.

November 9—**Pediatric Pain Management in Managed Care Environment**. Children's Hospital and Health Center at Corning Labs Conference Center, San Diego. Sat. 7 hrs, $85. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

December 7—**Fifteenth Annual Binational Pediatric Conference.** Children's Hospital and Health Center at Mercy Hospital Education Center, San Diego. Saturday. 5 hrs, $45. Contact: Children's Hospital, Continuing Medical Education, 3020 Children's Way (5021), San Diego, 92123. (619) 576-4072.

January 15-18—**San Diego Cerebral Palsy Symposium.** Children's Hospital at San Diego Marriott Mission Valley. Wed-Sat. 21.5 hrs, $450-$495. Contact: Continuing Medical Education, 3020 Children's Way (5021), San Diego 92123. (619) 576-4072.

January 27-31— **San Diego Conference on Responding to Child Maltreatment.** Children's Hospital at Town and Country Hotel, San Diego. Mon-Fri. 30.5 hrs, $435. Contact: Registration Coordinator, Center for Child Protection, 3020 Children's Way (MC5016), San Diego 92123. (916) 495-4940.

PLASTIC SURGERY

October 17-20—**Minimally Invasive Techniques for Facial Rejuvenation.** UCSF at Embarcadero Hyatt Regency Hotel, San Francisco. Thurs-Sun. Contact: UCSF.

PSYCHIATRY AND NEUROLOGY

November 2-3—**Neurology Update.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 12 hrs, $350. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

November 8-10—**The 42nd Annual Group Therapy Symposium.** UCSF at Mark Hopkins Hotel, San Francisco. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 20-25—**Advanced Imaging of the Spine.** UCSD at Hotel del Coronado, Coronado. Sat-Thurs. 22.5 hrs, $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

August 15-18—**Minimally Invasive Therapy of the Brain.** UCSD at Ritz-Carlton Hotel, Marina del Rey. Thurs-Sun. 20 hrs, $495. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 24-25—**Neuroradiology Comprehensive Review.** UCSD at Hotel del Coronado, Coronado. Thurs-Fri. 25 hrs, $550. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 26-27—**16th Annual Comprehensive Review of Vascular & Interventional Radiology.** UCSD at Hotel del Coronado, Coronado. Sat-Sun. 14 hrs. $375. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

October 28-November 1—**21st Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, Coronado. Mon-Fri. 27 hrs, $575. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

SURGERY

July 8-13—**13th Superficial Anatomy and Cutaneous Surgery.** UCSD. Mon-Sat. 36 hrs, $1,395. Contact: UCSD.

August 2-3—**Second Annual Surgical Review Postgraduate Course: Review of Lower Gastrointestinal and Breast Diseases.** UCD at David Grant Medical Center, Fairfield. Fri- Sat. 14 hrs, $225. Contact: UCD.

August 16-18—**Minimally Invasive Therapy of the Brain.** American Association of Physician Specialists at Ritz-Carlton Hotel, Marina del Rey. Fri-Mon. 15.5 hrs, $395. Contact: Ryals & Associates, Inc, PO Box 1925, Roswell, GA 30077-1925. (770) 641-9773.

January 4-8—**Temporal Bone Surgical Dissection Course.** The House Ear Institute, Los Angeles. Sat-Wed. 48 hrs, $1,300. Contact: House Ear Institute, 2100 W Third St, Los Angeles 90057. (213) 483-4431, ext 7079.

UROLOGY

October 5-9—**11th Combined Skin Pathlogy Course & Workshop in Dermatopathology**. UCSD at San Diego Princess. Sat-Wed. 37 hrs, $600. Contact: UCSD.

November 3-7—**VII World Meeting on Impotence.** American Urological Association and UCSF at Sheraton Palace, San Francisco. Mon-Thurs. $400-$475. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

July 10—**Pre-ACLS Workshop**. American Heart Association at San Leandro. Wed. 6 hrs, $50-$70. Contact: CPR Seminars, (510) 632-6135.

July 10 and 21—**ACLS Provider Course.** American Heart Association at San Francisco. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135

July 19—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs, $100.

August 8-11—**38th Annual Postgraduate Refresher Course—Reading Retreat.** USC at the Lodge at Koele, Lanai, Hawaii. Fri. 8 hrs, $100. Contact: USC.

August 11-21—**38th Annual Postgraduate Refresher Course.** USC at the Maui Westin Hotel, Maui, and Marriott Hotel, Kauai, Hawaii. 10 days. 80 hr, $640. Contact: USC.

August 17-18—**PALS Certification.** American Heart Association at San Leandro. Sat-Sun. 14 hrs, $250. Contact: CPR Seminars, (510) 632-6135.

(Continued on Page 478)

104th ANNUAL MEETING SCHEDULE

IDAHO MEDICAL ASSOCIATION

JULY 25-27, 1996—SUN VALLEY, IDAHO

AN INVITATION TO SUN VALLEY

We are pleased to extend you a cordial invitation to attend the 104th Annual Meeting of the Idaho Medical Association in the beautiful setting of Idaho's Sun Valley. An excellent scientific session has been planned that should appeal to all types of physicians—family practitioners and specialists alike. It should be a good opportunity not only to enjoy beautiful Sun Valley but also to receive 6 credit hours of Category I CME.

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JESSE GREENBLATT, MD, MPH, State Epidemiologist, State of Idaho, Department of Health and Welfare, Boise, Idaho

N. LEE SMITH, MD, Associate Professor of Medicine (Clinical), Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah

JAMES BLACKMAN, MD, Idaho Clinical Coordinator, Wami (Idaho, Center for Clinical Medical Education), University of Washington School of Medicine

SCIENTIFIC SESSION

Friday, July 26, 1996

7:30 am	Technical Exhibits Open Continental Breakfast
8:15 am	Welcome—David Anderson, MD Idaho Medical Association, President
8:30-9:30 am	"Prevention in Clinical Practice: The Need For A New Paradigm" Tom Vogt, MD
9:30 am	Recess to View Exhibits
10:00-noon	"Internet 101: A First Ride on the Infobahn" "Medicine in Cyberspace" Hans Sieburg, MD
12:00-1:30 pm	Alliance Luncheon (Spouses Welcome) Speaker: Congressman Mike Crapo (Invited)
1:30-2:30 pm	"Emerging Infectious Diseases in Idaho" Jesse Greenblatt, MD
2:30-3:30 pm	"The Medical Importance and Management of Obesity" N. Lee Smith, MD
3:30 pm	Break
3:45-4:45 pm	"Diseases of Antiquity" James Blackman, MD

Saturday, July 27, 1996

10:00 am	Raymond D. Strother Political Consultant, Washington D.C.

FOR MORE INFORMATION CALL THE IDAHO MEDICAL ASSOCIATION AT 208-344-7888

(Continued from Page 476)

August 19 and 22—**ACLS Instructor Training.** American Heart Association at San Leandro. Mon and Thurs. 10 hrs, $195. Contact: CPR Seminars, (510) 632-6135.

September 12 and 19—**Arrhythmia Recognition.** American Heart Association at San Leandro. Thurs. 10 hrs, $120. Contact: CPR Seminars, (510) 632-6135.

September 16, 18, 24, 26—**CLS Provider Training.** American Heart Association at San Leandro. Mon and Wed, Tues and Thurs. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135.

October 18—**ACLS Recertification.** American Heart Association at San Francisco. Fri. 6 hrs, $100. Contact: CPR Seminars, (510) 632-6135.

October 19-20—**ACLS Provider.** American Heart Association at San Francisco. Sat-Sun. 16 hrs, $170. Contact: CPR Seminars, (510) 632-6135.

October 29-31—**ABC's Second Annual Telemedicine and Telehealth Conference.** UCD at Anaheim Convention Center. Tues-Thurs. $450-$550. Contact: UCD, (800) 829-3400.

December 12-14—**Diagnosis and Treatment of Back Pain—The Next Level.** St Mary's Hospital at Stanford Court Hotel, San Francisco. Thurs-Sat. Contact: Aubrey A. Swartz, MD, American Back Society, St Joseph's Professional Center, 2647 E 14th St, Ste 401, Oakland 94601. (510) 536-9929.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

July 14-19—**32nd Annual Internal Medicine Program.** University of Colorado at YMCA of the Rockies, Estes Park. Sun-Fri. Contact: U of Colo.

July 22-26—**Renal Disease and Electrolyte Disorders.** University of Colorado at Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 26-27—**Adenocarcinoma of the Prostate.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

July 31-August 3—**Musculoskeletal Infection Society Open Annual Scientific Meeting.** University of Colorado Health Sciences Center at Snowmass Village, Snowmass. Wed-Sat. Contact: U of Colo.

August 4-9—**21st Annual Primary Musculoskeletal Care Conference.** University of Colorado Health Sciences Center at Breckenridge. Sun-Fri. Contact: U of Colo.

August 8-11—**Sixth Annual CME Conference: Women Physicians Finding a Balance, "Keeping the Spark Alive."** Rose Medical Center at Marriott Mountain Resort, Vail. Thurs-Sun. Contact: Ann Wilcox, Rose Medical Center Physician Support Services, (800) 525-1253 or (303) 770-2220.

August 11-13—**First Annual Aspen Brain Tumor Symposium.** University of Colorado at Given Institute, Aspen. Contact: U of Colo.

September 18-21—**Enhancing Quality and Value in Cardiovascular Care.** University of Colorado Health Sciences Center at Vail. Thurs-Sat. Contact: U of Colo.

October 28-November 1—**42nd Annual Family Practice Review (Repeat of June program).** University of Colorado Health Sciences Center at Denver. Mon-Fri. Contact: U of Colo.

December 6-7—**5th Update in Infectious Disease: Bugs and Drugs in the '90s.** University of Colorado Health Sciences Center at Denver. Fri-Sat. Contact: U of Colo.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Every Second Wednesday of the Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 8-11—**39th Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Ruidoso. Mon-Thurs. Contact: Ann Woodrow, CAE, NMAFP, 2309 Renard SE, Albuquerque 87106. (505) 243-4560.

July 11-14—**New Choices, New Challenges, Psychopharmacology in the Primary Care Setting.** La Fonda Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 24-28—**Podiatric Surgical Seminar.** Hotel Santa Fe, Santa Fe. Wed-Thurs. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

July 26-28—**How to Diagnose and Treat Arrhythmias for the Primary Care Physician.** Eldorado Hotel, Santa Fe. Fri-Sun. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

August 2-4—**Practical Pediatrics.** La Fonda Hotel, Santa Fe. Fri-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

(Continued on Page 549)

The Western Journal of Medicine and the California Medical Association Foundation would like to acknowledge and thank Kouichi R. Tanaka, MD, and the Governors of the California Chapter of the American College of Physicians for their generous donation to the CMA Foundation's "Western Journal of Medicine—New Directions Fund."

A special welcome to all Associate Members of the California Chapter of the American College of Physicians.

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Since education of physicians is one of our highest priorities, we hope that you will participate in the activities of your Region and other Regions of the California Chapter as well as the Annual Session of the American College of Physicians.

To make a tax-deductible donation to the "WJM New Directions Fund" or for more information about the CMA Foundation, please write to the California Medical Association Foundation, PO Box 7690, San Francisco, CA 94120-7690 or call 415.882.3333.

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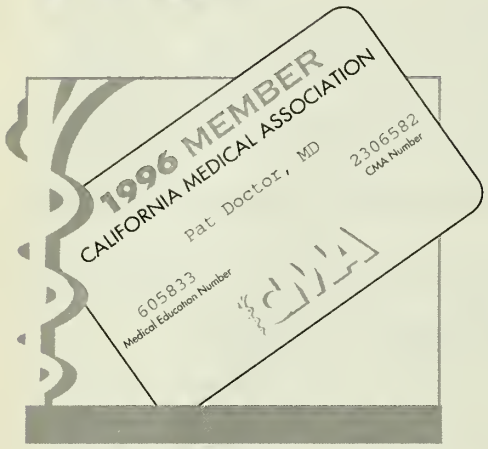

Our medical profession needs to strengthen by joining together as one voice. The **California Medical Association** recognizes this and is restructuring to become more responsive to physicians and patients.

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To receive additional membership information and applications for your solicitations, contact your local county medical society:

Alameda-Contra Costa Medical Association — (510) 654-5383
Butte-Glenn Medical Society — (916) 342-4296
Fresno-Madera Medical Society — (209) 224-4224
Humboldt-Del Norte Medical Society — (707) 442-2367
Imperial County Medical Society — (619) 337-5807
Inyo-Mono County Medical Society — (619) 872-1780
Kern County Medical Society — (805) 325-9025
Kings County Medical Society — (209) 582-6793
Lassen-Plumas-Modoc-Sierra County Med. Soc. — (916) 258-4116
Los Angeles County Medical Association — (213) 483-1581
Marin Medical Society — (415) 924-3891
Mendocino-Lake County Medical Society — (707) 462-1694
Merced-Mariposa Medical Society — (209) 723-2976
Monterey County Medical Society — (408) 455-1833
Napa County Medical Society — (707) 255-3622
Orange County Medical Association — (714) 978-1160
Placer-Nevada County Medical Society — (916) 885-3951
Riverside County Medical Association — (909) 686-3342
Sacramento-El Dorado Medical Society — (916) 452-2671
San Benito County Medical Society — (408) 637-5711
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Shasta-Trinity County Medical Society — (916) 241-6834
Siskiyou County Medical Society — (916) 926-3171
Solano County Medical Society — (707) 425-7267
Sonoma County Medical Association — (707) 525-4319
Stanislaus Medical Society — (209) 527-1704
Tehama County Medical Society — (916) 529-4362
Tulare County Medical Society — (209) 627-2262
Tuolumne County Medical Society — (209) 532-4843
Ventura County Medical Society — (805) 656-3407
Yolo County Medical Society — (916) 753-3000
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Article

Human T-Lymphotropic Virus Type II Seroprevalence Among Emergency Department and Clinic Patients

DANIEL AGRANOFF, MD; KAREN VARNEY; HASSAN KHAYAM-BASHI, PhD; *and* EDWARD L. MURPHY, MD, MPH, *San Francisco, California*

To determine the seroprevalence of human T-lymphotropic virus types I and II (HTLV-I and HTLV-II) among emergency department and clinic patients at a San Francisco, California, hospital, consecutive patients from 4 outpatient settings—emergency department, medical clinic, antenatal clinic, and neighborhood health centers—were tested for antibody to 1 of the viruses using an enzyme-linked immunosorbent assay and Western blot test. Of 4,019 patients, 169 (4.2%) had antibody to HTLV-I or -II; the seroprevalence of HTLV-II (3.5%) was greater than that of HTLV-I (0.7%). Seroprevalence for HTLV-II was highest in the emergency department (6.9%) and neighborhood clinics (3.9%) and in those aged 30 to 59 years (5.9%). Crude HTLV-II prevalence was higher in men (5.2%) than in women (2.2%), but sex was not an independent risk factor after age and location were controlled for. This study showed a higher seroprevalence of HTLV-I and HTLV-II among outpatients than did previous studies, probably because of a high proportion of injection-drug users. In view of the recent description of HTLV-II–associated myelopathy, studies of neurologic disease in this population may be warranted. HTLV-II should be included in the list of occupationally transmitted infections for hospitals with many injection-drug–using patients.

(Agranoff D, Varney K, Khayam-Bashi H, Murphy EL: Human T-lymphotropic virus type II seroprevalence among emergency department and clinic patients. West J Med 1996; 164:481-485)

Human T-lymphotropic virus types I and II (HTLV-I and HTLV-II) are human retroviruses sharing approximately 60% nucleotide homology. There is strong evidence that HTLV-I is the etiologic agent in adult T-cell leukemia[1-3] and in HTLV-I–associated myelopathy, a chronic demyelinating neurologic disease.[4] There is recent evidence that HTLV-II is also associated with a myelopathy similar to HTLV-I–associated myelopathy.[5-7] Infection with HTLV-I is endemic in areas of southern Japan, sub-Saharan Africa, the Caribbean basin, and the southeastern United States; the country-specific incidence rates of adult T-cell leukemia and HTLV-I–associated myelopathy show a similar geographic distribution. In the United States, the combined prevalence of HTLV-I and -II infection among volunteer blood donors has been found to be 0.02% to 0.04%,[8] and the risk factors for HTLV-I infection are a relevant ancestry or sexual contact with persons from endemic areas. Half to two thirds of cases of HTLV infection in the United States, however, have been attributed to HTLV-II,[9,10] and the principal risk factors in this case are injection-drug use,[9-13] sexual contact with an injection-drug user, and Native American ethnicity.[14-17]

A few studies have examined the prevalence of HTLV infection among emergency department patients in several US cities, motivated in part by the possible risks posed to emergency department staff. Prevalence rates of 1% to 2% for HTLV-I and -II have been reported,[18-20] and associations with known risk factors have been confirmed. There are few data on other outpatient subgroups, however. In this study we measured the prevalence of HTLV seropositivity in outpatients in emergency departments and medical, antenatal, and community clinics at a large public hospital in San Francisco, California. The intention was to obtain baseline epidemiologic data on seroprevalence among different patient subgroups to help direct the focus of future, more in-depth studies.

Patients and Methods

Subjects and Specimens

Between June 1989 and November 1990, we studied patients at four types of outpatient departments associated with San Francisco General Hospital Medical Center, namely the emergency department, general medical clinic, antenatal clinic, and two neighborhood health cen-

From the Department of Laboratory Medicine, University of California, San Francisco (UCSF), and San Francisco General Hospital Medical Center. Dr Agranoff is currently affiliated with St George's Hospital, London, England.

This work was supported in part by Academic Senate and Research Evaluation and Allocation Committee grants from UCSF and by the Charles E. Culpeper Foundation. Dr Murphy is a Charles E. Culpeper Medical Scholar.

Reprint requests to Edward L. Murphy, MD, MPH, Dept of Laboratory Medicine, UCSF, Box 0884, San Francisco, CA 94143-0884.

ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
HTLV-I, -II = human T-lymphotropic virus types I, II

ters. Residual serum or plasma specimens that had been drawn initially for a specific medical indication were collected sequentially from the clinical laboratory of the hospital. Collection continued until about 1,000 specimens had been obtained from each location. Only information available on the specimen label, namely, age, sex, hospital number, and clinic of origin, was recorded. Duplicate specimens from the same patient were discarded by culling repeat hospital numbers. We did not gather data on the proportion of patients at each clinic who had blood specimens drawn. The study protocol was approved by the University of California, San Francisco, Committee on Human Research.

Serologic Testing

Serum from each specimen was tested with an HTLV-I enzyme-linked immunosorbent assay (ELISA; DuPont, Wilmington, Delaware). A lower ELISA cutoff threshold of 0.7 times the manufacturer's recommended cutoff was used to enhance the sensitivity of the assay for cross-reactive HTLV-II antibody, as recommended elsewhere.[21] Reactive specimens were retested in duplicate. Those with at least two out of three positive results on ELISA were then tested using a Western blot containing HTLV-I whole virus lysate plus recombinant HTLV-I p21 envelope protein (Cambridge Biotech, Rockville, Maryland). This Western blot has a sensitivity of 97.4% and a specificity of 97.5%.[22] A patient's serologic status was defined on the basis of the Western blot using the following criteria: p21env or gp46 plus p19 or p24 is seropositive; any bands less than the above criteria were classified as seroindeterminate; no Western blot bands were considered seronegative. A qualitative assessment of viral type was based on the relative intensities of the p19 and p24 bands,[23] namely, p19 of equal or stronger intensity than the p24 band equals HTLV-I; a p19 band of weaker intensity than the p24 band equals HTLV-II.

Data Analysis

Univariate and stratified frequencies were computed using a standard statistical package (SAS-PC version 6.4, Cary, North Carolina). A logistic regression analysis using the SAS PROC LOGIST function was done to estimate independent odds ratios for the various predictors of HTLV seropositivity.

Results

A total of 4,019 specimens was obtained, of which 66 lacked data on sex, 60 lacked data on age, and 1 lacked data on location. There were 1,686 (42.7%) males and 2,267 (57.3%) females, with mean ages of 44.8 years and 38.5 years, respectively (Table 1). Patients attending the medical outpatient clinic were generally older than those in the neighborhood clinics or the emergency department, whereas those attending the antenatal clinic were the youngest. Women predominated in the antenatal clinic, men in the emergency department, and the medical clinic and neighborhood clinics had more equal sex distributions.

Of 4,019 patients, 169 (4.2%) had Western blot results positive for HTLV-I or -II, and 35 (0.9%) were seroindeterminate on the Western blot test. Of specimens with ELISA reactivity greater than the manufacturer's cutoff, 89.1% were subsequently found to be positive on Western blot compared with 66.7% of specimens with optical densities between 0.7 and 1 times the cutoff. Most positive specimens were reactive to several viral proteins; only eight positive specimens had a p21env/p24-only pattern, and none had a p21env/p19-only pattern. According to the intensity of the p19 and p24 Western blot bands, 28 (0.7%) had HTLV-I antibody whereas 141 (3.5%) had HTLV-II antibody, giving a ratio of HTLV-II to HTLV-I of 4.9:1. Polymerase chain reaction analysis was subsequently done on 11 randomly selected HTLV-I– or -II–seropositive specimens from the same population. Lysates of peripheral blood mononuclear cells were amplified with primers to the common *pol* region of both HTLV types, followed by hybridization with probes to type-specific sequences within the amplified regions. One specimen hybridized to HTLV-I sequences, eight to HTLV-II sequences, and two to both HTLV-I and -II probes, suggesting either cross-reactivity or coinfection with both HTLV types. All hybridization signals were strong.

Seroprevalence for both viruses was higher among men: 0.9% for HTLV-I and 5.2% for HTLV-II, compared with 0.5% and 2.2% in women, respectively. Figure 1 shows HTLV-I and -II seroprevalence by age and sex. The

TABLE 1.—*Study Population by Clinic* and Sex†*

Clinic	Men No.	Men Mean Age, yr (SD)‡	Women No.	Women Mean Age yr, (SD)‡
Antenatal clinic	1	22 (--)	1,012	28.3 (8.8)
Medical clinic	533	49.9 (15.6)	508	52.2 (14.9)
Neighborhood clinics	373	49.0 (17.3)	492	44.9 (18.0)
Emergency department	779	39.2 (14.5)	254	39.7 (17.8)
All subjects	1,686	44.8 (16.3)	2,267	38.5 (16.9)

SD = standard deviation

*Clinic location was missing on 1 subject.
†Sex information was missing on 66 subjects.
‡Missing ages on 60 subjects were excluded from the calculation of the means.

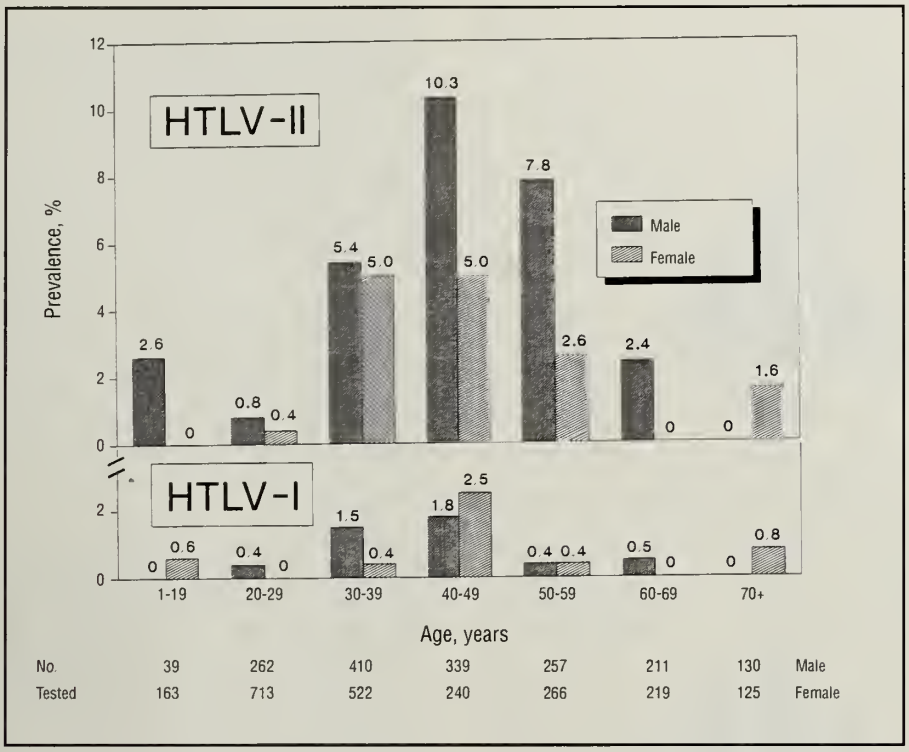

Figure 1.—The graph shows the age- and sex-specific seroprevalence of human T-lymphotropic virus types II (HTLV-II) and I (HTLV-I) among emergency department and clinic patients in San Francisco, California. The number of subjects in each age and sex subgroup is indicated across the bottom of the figure.

seroprevalence for HTLV-II was low in the youngest and oldest age groups, but reached maximum levels in the 40- to 49-year age group for men and perhaps slightly younger for women. Most of the cases of infection were accounted for by the age groups between 30 and 59 years. The seroprevalence of HTLV-I followed a similar pattern, but with lower absolute values.

The highest prevalence of HTLV-II infection was found among emergency department patients (6.9%), followed by the neighborhood (3.9%) and medical (2.3%) clinics (Table 2). Only 0.9% of those attending the antenatal clinic were seropositive for HTLV-II. To look more closely at the emergency department and neighborhood clinic populations, in which the highest prevalences occur, the data from these two locations were stratified by age and sex (Figure 2). As in the overall results, the highest age-specific prevalence of HTLV-II infection occurred in the 30- to 59-year age group in both the emergency department (10%) and in the neighborhood clinic (6.8%). Within the 30- to 59-year age group, HTLV-II seropositivity was significantly higher among women attending the emergency departments than among those attending the neighborhood clinics (12% versus 5.3%, $\chi^2 = 5.42$, degrees of freedom [df] = 1, $P < .02$) while for men there was little difference (9.3% versus 8.5%, $\chi^2 = 0.15$, $df = 1$,

TABLE 2.—*Human T-Lymphotrophic Virus Types I and II (HTLV-I and -II) Seroprevalence by Type of Outpatient Facility*

	Patients		
		No. Seropositive (%)	
Location	*No.*	*HTLV-I*	*HTLV-II*
Emergency department	1,038	13 (1.3)	72 (6.9)
Neighborhood clinic	922	8 (0.9)	36 (3.9)
Medical clinic	1,044	5 (0.5)	24 (2.3)
Antenatal clinic	1,014	2 (0.2)	9 (0.9)
All subjects	4,018*	28 (0.7)	141 (3.5)

*Data on type of facility were missing for 1 subject.

TABLE 3.—*Independent Risk Factors for Human T-Lymphotrophic Virus Types I and II (HTLV-I and -II) Seropositivity as Determined by Logistic Regression Analysis*

	HTLV-I		HTLV-II	
Variable	*Odds Ratio*	*95% CI*	*Odds Ratio*	*95% CI*
Age, yr				
<30	1.0	--	1.0	--
30-59	5.6	(1.3, 24.6)	10.1	(4.4, 23.2)
≥60	1.5	(0.2, 11.3)	1.7	(0.6, 5.2)
Sex				
Male	1.0	--	1.0	--
Female	1.1	(0.5, 2.6)	0.8	(0.6, 1.3)
Location				
Medical clinic	1.0	--	1.0	--
Emergency department	3.0	(1.0, 8.9)	3.0	(1.9, 5.0)
Neighborhood clinic	1.6	(0.5, 5.4)	2.1	(1.2, 3.5)
Antenatal clinic	0.6	(0.1,3.3)	0.7	(0.3, 1.5)

CI = confidence interval

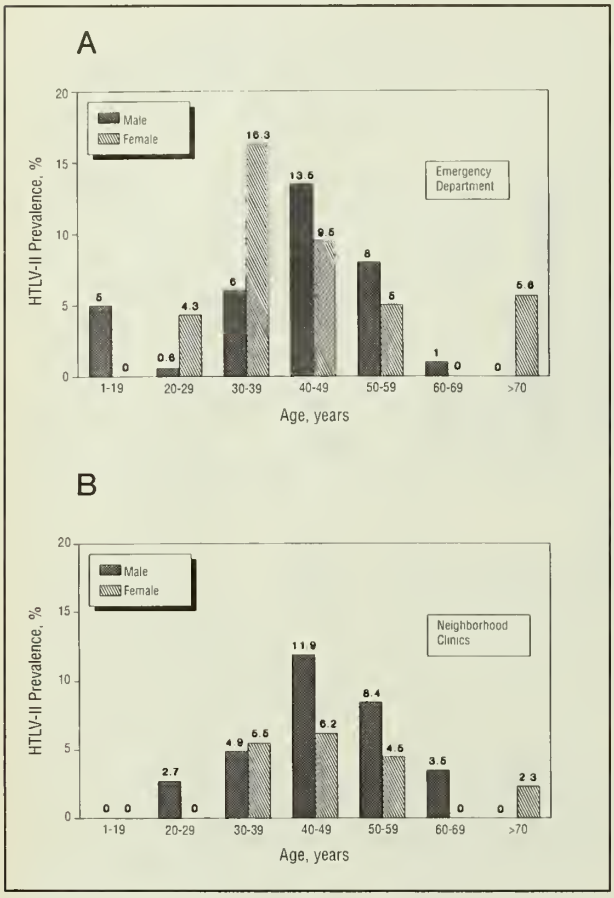

Figure 2.—The graphs show age- and sex-specific seroprevalence of human T-lymphotropic virus type II (HTLV-II) for the 2 locations with the highest prevalence within the study, namely, emergency department patients **(A)** and patients at 2 neighborhood health clinics affiliated with the same hospital **(B)**.

$P < .5$). Estimates of age, sex, and clinic-specific HTLV-I seroprevalence were less stable because of a lower overall prevalence, but a similar concentration of seropositive tests within 30- to 59-year-old emergency department patients was seen.

To obtain unbiased estimates of the risk associated with each variable under study, we did a logistic regression analysis (Table 3). Being between 30 and 59 years old and being a patient in the emergency department or neighborhood clinic were significantly associated with HTLV-II infection, but gender was not. The risk associated with HTLV-I infection differed in that neighborhood clinic attendance was not associated with seropositivity.

Discussion

In this study we tested surplus blood specimens from four types of outpatient facilities to gain an impression of HTLV-I and -II seroprevalence among San Francisco outpatients and to determine the relative prevalence of the two viruses. The latter distinction is important because HTLV-I is associated with two important diseases—adult T-cell leukemia and HTLV-I–associated myelopathy—with lifetime risks of 4%[24] and 0.24 to 2.4,[25,26] respectively. Infection with HTLV-II may also be associated with HTLV-I–associated myelopathy, although at a lower prevalence per seropositive patients than for HTLV-I.[26]

Three previous studies have looked at HTLV-I and -II infection among emergency department patients. These earlier studies revealed prevalences of 1.1% in Baltimore,[18] 2.1% in Detroit,[19] and 2% in California,[20] although in the California study ten emergency departments in different parts of the state were examined, with prevalence rates varying between 0% and 4%. This variation presumably reflects the relative representation of factors associated with HTLV-II infection, such as injection-drug use and ethnicity, at each location. These prevalence rates are some 50 to 200 times greater than the 2.5 per 10,000 HTLV-I and -II seroprevalence among random blood donors in the United States,[8] although it should be noted that the latter represent a self-selected group that is probably less likely to be infected than other sections of the community.

Our study, on the other hand, has shown a markedly higher combined HTLV-I and -II seroprevalence than has hitherto been recorded in an emergency department population (8.2%), of which almost five sixths was attributable to HTLV-II. It seems unlikely that our sampling method could have been more biased than those of previous studies because we sampled consecutively and excluded duplicate specimens. It is also possible that our serologic testing was more sensitive, especially because we specifically used a lower ELISA cutoff than recommended by the manufacturer. On the other hand, our prevalence estimate for HTLV-II may be falsely low because we differentiated HTLV-II from HTLV-I based on the HTLV-I Western blot pattern rather than by using type-specific reagents that have since become available. The most probable explanation for our findings is that our emergency department (and neighborhood clinic) populations included a higher proportion of persons with injection-drug use or other high-risk behaviors than the other studies. The demographic correlates of HTLV-II seropositivity that we observed are similar to those seen in studies of injection-drug use alone.[27,28]

With regard to antenatal clinic attenders, our finding of a 1.1% combined HTLV-I and -II seroprevalence is higher than rates of 0.26% and 0.2% reported from two studies in London in 1980 and 1990, respectively.[29,30] It is possible that our study included more women with HTLV-II–related risk behaviors of injection-drug use or sex with an injection-drug user, whereas the British studies may have included more Caribbean immigrants at risk for HTLV-I infection.

Our finding that HTLV-I and -II seroprevalence is low in young patients, greatest in the 30- to 59-year age group, and lower in the elderly is likely to be due to a combination of epidemiologic factors. First, HTLV-I and -II seroprevalence increases with age among injection-drug users, and the duration of heroin abuse rather than age itself is the strongest risk factor.[27] Persons older than 50 years who inject drugs had the highest HTLV-I and -II seroprevalence in the above-referenced study, although there were few injection-drug users of this age. Second,

there may be relatively fewer injection-drug users among older outpatients in the current study because drug injection is less common among persons born before the 1930s, and those who did inject drugs are less likely to survive into older age. We also found that HTLV-II seropositivity was higher among women attending emergency departments than among those attending the neighborhood clinics (no difference among men), suggesting that women with HTLV-II risk behaviors preferentially attended emergency departments.

Emergency department staff may be at risk of occupationally acquired HTLV-II or HTLV-I, in addition to other parenterally acquired infections.[18] At least two cases of possibly occupationally acquired HTLV-I or -II infection without other risk factors have been reported, namely, one in an HTLV-I–infected Belgian midwife who worked in Africa[31] and one in an HTLV-II–infected dentist in San Francisco.[10] If we assume that the risk of acquiring HTLV infection per puncture with a blood-contaminated hollow needle is the same as the 0.2% estimate for the human immunodeficiency virus,[32] then occupationally acquired HTLV-I or -II poses a small additional risk for emergency department staff. Universal precautions against blood-borne infection should be reinforced.

In conclusion, we have demonstrated a high seroprevalence of HTLV-II and, to a lesser degree, HTLV-I among outpatients at a public hospital and its neighborhood clinics. This high prevalence is most probably a reflection of a high proportion of injection-drug use among the population studied. Because both HTLV-I and HTLV-II cause disease in a small percentage of infected persons, physicians practicing in urban America should consider HTLV-I or -II infection in their differential diagnosis of spastic paraparesis and lymphoma. Finally, infection with HTLV-I and HTLV-II should be included in existing programs for the surveillance and prevention of occupationally acquired hepatitis B, hepatitis C, and human immunodeficiency virus.

Acknowledgment

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REFERENCES

1. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 1980; 77:7415-7419

2. Hinuma Y, Nagata K, Hanaoka M, et al: Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci USA 1981; 78:6476-6480

3. Murphy EL, Blattner WA: HTLV-I-associated leukaemia: A model for chronic retroviral diseases. Ann Neurol 1988; 23:S174-S180

4. Gessain A, Barin F, Vernant JC, et al: Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. Lancet 1985; 2:407-410

5. Hjelle B, Appenzeller O, Mills R, et al: Chronic neurodegenerative disease associated with HTLV-II infection. Lancet 1992; 339:645-646

6. Murphy EL, Engstrom JW, Miller K, Sacher RA, Busch MP, Hollingsworth CG, and the REDS Investigators: HTLV-II associated myelopathy in 43-year-old woman (Letter). Lancet 1993; 341:757-758

7. Jacobson S, Lehky T, Nishimura M, Robinson S, McFarlin DE, Dhib-Jalbut S: Isolation of HTLV-II from a patient with chronic, progressive neurological disease clinically indistinguishable from HTLV-I-associated myelopathy/tropical spastic paraparesis. Ann Neurol 1993; 33:392-396

8. Williams AE, Fang CT, Slamon DJ, et al: Seroprevalence and epidemiological correlates of HTLV-I infection in US blood donors. Science 1988; 240: 643-646

9. Lee HH, Swanson P, Rosenblatt JD, et al: Relative prevalence and risk factors of HTLV-I and HTLV-II infection in US blood donors. Lancet 1991; 337:1435-1439

10. Eble BE, Busch MP, Guiltinan AM, Khayam-Bashi H, Murphy EL: Determination of human T lymphotropic virus type by polymerase chain reaction and correlation with risk factors in northern California blood donors. J Infect Dis 1993; 167:954-957 [erratum published in J Infect Dis 1993; 168:262]

11. Robert-Guroff M, Weiss SH, Giron JA, et al: Prevalence of antibodies to HTLV-I, -II, and -III in intravenous drug abusers from an AIDS endemic region. JAMA 1986; 255:3133-3137

12. Ehrlich GD, Glaser JB, LaVigne K, et al: Prevalence of human T-cell leukaemia/lymphoma virus (HTLV) type II infection among high risk individuals: Type-specific identification of HTLVs by polymerase chain reaction. Blood 1989; 74:1658-1664

13. Lee H, Swanson P, Shorty VS, Zack JA, Rosenblatt JD, Chen ISY: High rate of HTLV-II infection in seropositive IV drug abusers in New Orleans. Science 1989; 244:471-475

14. Hjelle B, Ray M, Swenson S, Mertz G, Key C, Allen S: Incidence of hairy cell leukaemia, mycosis fungoides, and chronic lymphocytic leukaemia in first known HTLV-II-endemic population. J Infect Dis 1991; 163:435-440

15. Lairmore MD, Jacobson S, Gracia F, et al: Isolation of human T-cell lymphotropic virus type 2 from Guaymi Indians in Panama. Proc Natl Acad Sci USA 1990; 87:8840-8844

16. Maloney EM, Biggar RJ, Neel JV, et al: Endemic human T-cell lymphotropic virus type II infection among isolated Brazilian Amerindians. J Infect Dis 1992; 166:100-107

17. Levine PH, Jacobson S, Elliott R, et al: HTLV-II infection in Florida Indians. AIDS Res Hum Retroviruses 1993; 9:123-127

18. Lewandowski C, Ognjan A, Rivers E, et al: Health care worker exposure to HIV-I and HTLV-I/II in critically ill, resuscitated emergency department patients. Ann Emerg Med 1992; 21:1353-1359

19. Kelen GD, DiGiovanna TA, Lofy L, et al: Human T-lymphotropic virus (HTLV I-II) infection among patients in an inner-city emergency department. Ann Intern Med 1990; 113:368-372

20. Rhee KJ, Albertson TE, Kizer KW, Burns MJ, Hughes MJ, Ascher MS: A comparison of HIV-1, HBV and HTLV-I/II seroprevalence rates of injured patients admitted through California emergency departments. Ann Emerg Med 1992; 21:397-401

21. Lipka JJ, Parker JL, Foung SKH: Enhancing the sensitivity of HTLV-I immunoassays. *In* Blattner WA (Ed): Human Retrovirology: HTLV. New York, NY, Raven Press, 1990, pp 409-417

22. Kleinman SH, Kaplan JE, Khabbaz RF, Calabro MA, Thomson R, Busch M, and the Retrovirus Epidemiology Donor Study Group: Evaluation of a p21e-spiked western blot (immunoblot) in confirming human T-cell lymphotropic virus type I or II infection in volunteer blood donors. J Clin Microbiol 1994; 32:603-607

23. Wiktor SZ, Alexander SS, Shaw GM, et al: Distinguishing between HTLV-I and HTLV-II by western blot (Letter). Lancet 1990; 335:1533

24. Murphy EL, Hanchard B, Figueroa J, et al: Modelling the risk of adult T-cell leukaemia/lymphoma in persons infected with human T-lymphotropic virus type-I. Int J Cancer 1989; 43:250-253

25. Kaplan JE, Osame M, Kubota H, et al: The risk of development of HTLV-I-associated myelopathy/tropical spastic paraparesis among persons infected with HTLV-I. J Acquir Immune Defic Syndr 1990; 3:1096-1101

26. Murphy EL, Fridey J, Smith JW, et al: High prevalence of HTLV-associated myelopathy (HAM) among subjects infected with HTLV-I and HTLV-II (Abstr S-263). Transfusion 1993; 33(9 suppl):68S

27. Feigal E, Murphy EL, Vranizan K, et al: Human T cell lymphotropic virus types I and II in intravenous drug users in San Francisco: Risk factors associated with seropositivity. J Infect Dis 1991; 164:36-42

28. Thiede H, Harris NV, McGough JP, Roberts B, Khabbaz RF, Kaplan JE: Prevalence of HTLV types I and II among drug users in King County, Washington. West J Med 1994; 160:540-544

29. Tosswill JH, Ades AE, Peckham C, Mortimer PP, Weber JN: Infection with human T cell leukaemia/lymphoma virus type I in patients attending an antenatal clinic in London. BMJ 1990; 301:95-96

30. Banatvala JE, Chrystie IL, Palmer SJ, Kenney A: Retrospective study of HIV, hepatitis B, and HTLV-I infection at a London antenatal clinic (Letter). Lancet 1990; 335:859-860

31. Goubau P, Carton H, Cornet P, et al: Human T-cell lymphotropic virus type 1 infection and tropical spastic paraparesis in Belgian expatriates. J Med Virol 1992; 36:13-15

32. Fahrner R, Gerberding JL: Risk of HIV infection in health care workers. *In* Volberding PA, Jacobson MA (Eds): AIDS Clinical Review 1993/1994. New York, NY, Marcel Dekker, 1994, pp 239-252

Articles

Isoniazid-Related Fatal Hepatitis

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To describe the clinical and demographic characteristics of fatal hepatitis due to single-drug isoniazid preventive therapy for tuberculosis, we did a survey of cases from state health departments, published case reports, and reports to the Centers for Disease Control and Prevention from 1970 to 1992. Of 108 reported cases, some clinical information was available for 76. A medical review panel judged 39 of these deaths as probably due to isoniazid hepatitis and 23 deaths as possibly due to isoniazid hepatitis. Of the 62 probable and possible cases combined, 50 (81%) were female, 49 (79%) were non–Hispanic black or Hispanic, and 19 (31%) were younger than 35 years. The median duration of isoniazid preventive therapy before symptom onset was 16 weeks. Of the 60 cases with symptom information, 54 (90%) presented with jaundice. Of the 62 cases, 26 (42%) were monitored monthly in accordance with current recommendations, and 6 of the patients were younger than 35 years. We estimate that the rate of fatal isoniazid hepatitis among patients in the public sector was no greater than 4.2 per 100,000 persons beginning therapy and no greater than 7 per 100,000 persons completing therapy. Adherence to isoniazid preventive therapy guidelines apparently reduces, but does not eliminate, the risk of fatal hepatitis. Careful patient selection, education, and monitoring are critical for minimizing that risk.

(Millard PS, Wilcosky TC, Reade-Christopher SJ, Weber DJ: Isoniazid-related fatal hepatitis. West J Med 1996; 164: 486-491)

Since its introduction in 1952, isoniazid has been widely used as a single agent to prevent active tuberculosis in persons infected with *Mycobacterium tuberculosis*. It is currently the only agent approved by the US Food and Drug Administration (FDA) for that purpose. Early clinical trials demonstrated the effectiveness of isoniazid preventive therapy and failed to show clinically important toxicity.[1-3] Case series[4-6] and cohort studies[7-9] subsequently revealed, however, that administering isoniazid can rarely result in serious hepatotoxicity and death.

The Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, and the American Thoracic Society have recommended isoniazid preventive therapy, with interim modifications of the indications for its use, since 1965.[10-17] Isoniazid preventive therapy plays a large role both in the 1989 strategic plan to eliminate tuberculosis and the 1992 action plan to combat multidrug-resistant tuberculosis.[18-19] The increase in tuberculosis incidence rates since 1985 in the United States has prompted a renewed emphasis on tuberculin skin test screening and isoniazid preventive therapy.[20] In addition, isoniazid is effective in preventing tuberculosis in persons infected with the human immunodeficiency virus (HIV).[21] Reports of fatal isoniazid-associated hepatitis[22-24] have reignited debate about the widespread use of isoniazid preventive therapy.[25-27]

A recent search of available databases found 177 possible cases of fatal isoniazid hepatitis in the United States between 1965 and 1989.[28] The study lacked clinical information about the suspected cases, however, and the authors could not be certain that all had indeed taken isoniazid preventive therapy. Although published reports of specific cases typically include clinical information, they lack a uniform case definition, and they usually do not reflect a systematic case-finding effort.[29] In one report, the rate of fatal isoniazid hepatitis was estimated to be 14 per 100,000 persons who started isoniazid therapy.[28] In another the rate of fatal isoniazid hepatitis was estimated to be 1 per 100,000.[29] The limitations of these data result in considerable uncertainty concerning the magnitude of fatal liver toxicity from isoniazid preventive therapy.

As part of a CDC-sponsored study of risk factors for fatal hepatitis from isoniazid preventive therapy, we attempted to obtain clinical data for all suspected cases in the United States from 1970 to 1992 for subsequent review by an expert panel. We describe the cases and indicate where possible whether the CDC guidelines for isoniazid preventive therapy were followed.

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ABBREVIATIONS USED IN TEXT

AST = aspartate aminotransferase
CDC = Centers for Disease Control and Prevention
FDA = US Food and Drug Administration
HBsAg = hepatitis B surface antigen
HIV = human immunodeficiency virus
IQR = interquartile range

Patients and Methods

Potentially eligible cases were those who reportedly died in the United States of isoniazid-related hepatitis from 1970 to 1992 after receiving preventive therapy with isoniazid as the single antituberculous agent. In our search for cases, we pursued all those reported in the medical literature, and we contacted all state health departments and those of selected large metropolitan areas. When state health departments lacked a centralized reporting mechanism for suspected cases, we also contacted local health departments in areas that reported a substantial number of active tuberculosis cases. In addition, the CDC Division of Tuberculosis Elimination provided a list of suspected cases that had come to their attention. Although other data sources (such as the FDA Adverse Reaction Reporting System and the National Center for Health Statistics multiple-cause death tapes) include reports of possible cases,[28] patient identifiers that could lead to medical records are not available from these sources.

We collected all available clinical information for suspected cases: health department records, hospital records, histology reports and liver tissue sections, postmortem examination results, and death certificates. A medical panel reviewed all records and tissue sections for suspected cases; the panel comprised an infectious disease specialist, a gastroenterologist specializing in hepatology, and a pathologist skilled in liver diseases. The medical review panel used a case definition similar to that used in the US Public Health Service Cooperative Surveillance Study of 1971 to 1973[8]:

- Serum aspartate aminotransferase (AST) level at least five times the laboratory's normal level, or clinical symptoms likely due to hepatitis—jaundice, abdominal pain, nausea, vomiting, malaise, fever, headache, arthralgias, and myalgias.
- No evidence of other causes of hepatitis: blood tests positive for viral hepatitis, liver biopsies indicating hepatitis from toxins other than isoniazid, or reports of exposures to possibly fatal hepatotoxins near the time of diagnosis.

The panel assessed all available information, including the presence or absence of reported risk factors for isoniazid hepatitis, and classified cases as probable (death was likely due to isoniazid hepatitis), possible (consistent with isoniazid hepatitis, but other causes were possible), or unverifiable. High serum aminotransferase levels and tests negative for hepatitis B surface antigen (HBsAg) were generally necessary for a case to be judged probable. If the data were insufficient to exclude other causes (where only a death certificate was available) the case was judged unverifiable. In the few instances where panel members disagreed about case classification, the majority opinion ruled.

Results

Report of Cases

Authors of published articles and health department staff members reported 108 possible cases of fatal isoniazid-related hepatitis from 1970 to 1992. No state health department had comprehensive machine-retrievable records for identifying suspected cases, and manual searches to identify cases were rarely feasible because of the large volume of records. Therefore, the case-finding effort largely depended on the "institutional memory" of the health department staff. Our search uncovered considerably fewer cases than the 177 reported by others,[28] primarily because these authors included suspected cases from FDA Adverse Reaction Reports and from the National Center for Health Statistics mortality tapes (from which we could obtain no additional information). We also found that some of the previously reported suspected cases were ineligible for various reasons—such as nonfatal cases, duplicate reports, and suicide. In addition, previously reported suspected cases that were unknown to health department staff are excluded from our count, and several recent suspected cases not included previously are included here.

Descriptions of some suspected cases were published in more than one report. Several published reports described suspected cases that occurred in Maryland[6,8,30,31] and California.[22,31-34] Moreover, one of six cases reported jointly[6,8,30] had been described by others.[5,31] We obtained at least some records for 37 of the 49 published cases and for 39 additional suspected cases, for a total of 76 (70%) of the 108 suspected cases. The two most common reasons for failing to obtain documentation were the unavailability of the suspected case's name and the purging of old medical records. In at least five instances, ongoing lawsuits prevented our access to medical records.

Of the 76 suspected cases with documentation, 5 were ineligible: 2 had been treated with several antituberculous drugs, 2 had active tuberculosis, and 1 had no documented isoniazid exposure. The medical review panel therefore evaluated 71 suspected cases. A total of 39 deaths (55%) were judged as probably due to isoniazid hepatitis, 23 deaths (32%) were judged as possibly due to isoniazid hepatitis, and for 9 deaths (13%) the diagnosis was unverifiable.

Region IX of the CDC (Arizona, California, Hawaii, and Nevada) had the largest reported number of probable and possible cases, with 20 (32% of the 62 cases); all but 1 of these cases were from California. Of the 20 California cases reported earlier,[22] 11 were considered probable, 3 were possible, 2 were ineligible, and 4 had no available records. Region III (Delaware; Washington, DC; Maryland; Pennsylvania; Virginia; and West Virginia) and Region IV (Alabama, Florida, Georgia, Kentucky, Mississippi, North and South Carolina, and Tennessee) each had

13 cases, and no other CDC region reported more than 5 cases.

Characteristics of Cases

Three cases were known to have received isoniazid preventive therapy in the private sector; health departments apparently prescribed preventive therapy for all other cases. Table 1 shows the age and sex of the 39 probable and 23 possible cases. For probable and possible cases combined, 50 (81%) were female. Almost 80% of cases (49) were among non–Hispanic blacks or Hispanics (Table 2). For the 35 cases (56%) with a known birthplace, about half were foreign born (Table 3).

TABLE 1.—*Age and Sex of Probable and Possible Cases of Fatal Isoniazid Hepatitis, 1970 to 1992*

Sex	Age, yr	Probable Cases, No.	Possible Cases, No.	Total Cases, No.	(%)
Female	0-14	1	1	2	(4)
	15-34	10	2	12	(24)
	35-64	16	14	30	(60)
	65+	5	1	6	(12)
	Total female	32	18	50	(100)
Male	0-14	2	0	2	(17)
	15-34	1	2	3	(25)
	35-64	4	2	6	(50)
	65+	0	1	1	(8)
	Total male	7	5	12	(100)

Details of Isoniazid Preventive Therapy

Figure 1 shows the duration of isoniazid preventive therapy before the onset of hepatitis symptoms. Of the cases, 53 (85%) took isoniazid for 30 weeks or fewer before the onset of symptoms, and the median duration of isoniazid preventive therapy before symptoms began was 16 weeks. Of the 62 patients, 5 (8%) were known to have taken isoniazid intermittently during their course of preventive therapy, and 3 had previously received isoniazid preventive therapy.

TABLE 2.—*Race-Ethnicity of Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Race-Ethnicity	Probable Cases, No.	Possible Cases, No.	Total Cases, No.	(%)
White, non–Hispanic	7	5	12	(19)
Black, non–Hispanic	16	15	31	(50)
Hispanic	16	2	18	(29)
Asian	0	1	1	(2)
Total	39	23	62	(100)

TABLE 3.—*Foreign and US-Born Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Birthplace	Probable Cases, No.	Possible Cases, No.	Total Cases, No.	(%)
Foreign	14	5	19	(31)
United States	6	10	16	(26)
Unknown	19	8	27	(44)
Total	39	23	62	(100)

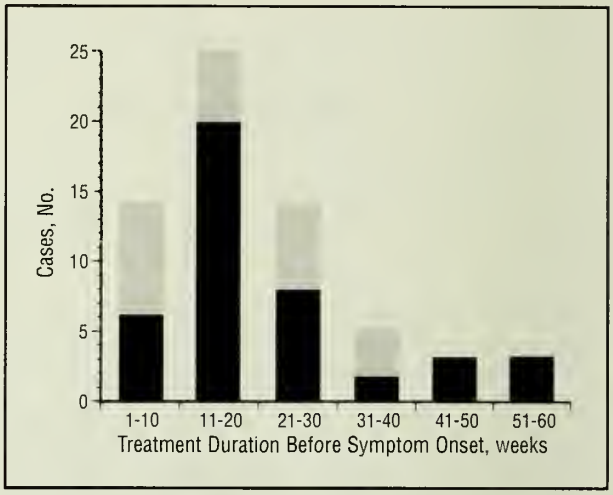

Figure 1.—The duration of isoniazid therapy in weeks before the onset of hepatitis symptoms is shown for probable (**shaded bars**) and possible (**black bars**) cases.

Among the 57 cases with data on the duration of therapy, treatment was continued as long as three months after the onset of symptoms (Figure 2). For two cases, however, isoniazid therapy reportedly ended before the onset of symptoms, and in an additional five cases (9%), therapy was reportedly stopped on the day symptoms began (Figure 2 does not include these 7 cases). In six of the cases (11%) shown in Figure 2, therapy was ended within three days of the onset of symptoms.

The monitoring of patients for adverse medication reactions was variable. For one possible and three probable cases (all occurring before 1982), follow-up was done once every three months. In contrast, 26 cases (42%) were monitored at least monthly; of these patients, 6 were younger than 35 years.

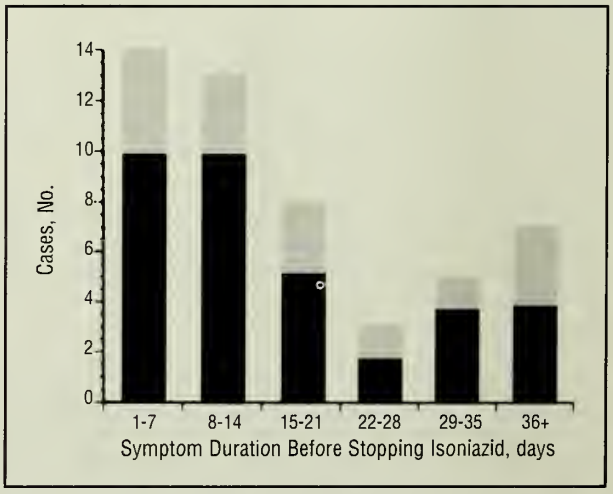

Figure 2.—The duration of hepatitis symptoms in days before stopping isoniazid therapy is shown for probable (**shaded bars**) and possible (**black bars**) cases. In addition, 5 patients stopped therapy on the day symptoms started, and 2 stopped before symptoms began.

Possible Contributing Factors

Because some medical records were incomplete, patients may have had contributing factors that did not appear in their charts. Thus, the reported numbers likely underestimate the actual numbers. In 14 cases (23%), the patients drank moderate to excessive amounts of alcohol or had a history of alcohol abuse. In 28 cases (45%), the patients were taking either possibly hepatotoxic drugs or drugs that could have exacerbated the hepatotoxicity of isoniazid. Possibly hepatotoxic drugs reported for at least two cases included acetaminophen (6 cases); aspirin (4 cases); hydrochlorothiazide (4 cases); and erythromycin, tetracycline, amitriptyline, and phenytoin (2 cases each).

No patients were known to have underlying disease associated with liver dysfunction or to have long-term exposure to environmental hepatotoxins. With the exception of one patient for whom the HBsAg result was unknown, all probable cases had negative HBsAg tests. Among possible cases, 13 were negative for HBsAg, 9 had unknown results, and 1 was positive. Hepatitis A immunoglobulin M antibodies were tested in 18 (46%) probable cases and in 3 (13%) possible cases; all tests were negative. Hepatitis C serologic testing was done for one probable and one possible case and was negative in both instances. The only case known to have been tested for HIV infection had a negative result.

Four women were pregnant at the time of starting isoniazid preventive therapy. In addition, a 23-year-old woman started isoniazid therapy when she was six months postpartum. She was observed monthly, hepatitis symptoms developed during the last month of the planned six-month course, and she continued isoniazid for three weeks after the onset of symptoms.

Clinical Course

Among the 60 probable and possible cases with available data about symptoms, 54 patients (90%) had jaundice on presentation and 30 (50%) presented with nausea. Other common symptoms at presentation included vomiting (25 [42%]), anorexia (23 [38%]), abdominal pain (22 [37%]), and dark urine (21 [35%]). Fifteen patients or fewer presented with changes in mental status, acholic stools, fever, or fatigue.

We could sometimes obtain only a single liver function test result, and that measure may not have corresponded to the patient's peak level. Furthermore, we often did not know the laboratory-specific normal ranges for aminotransferase levels. Nonetheless, the median peak reported AST level was 1,230 units (interquartile range [IQR], 636 to 2,478) in women (that is, 25% of women had levels below 636, and 25% had levels above 2,478) and 1,447 units (IQR, 1,200 to 3,455) in men. The median peak total serum bilirubin level was 28 mg per dl (480 μmol per liter) (IQR, 21 to 35 [360 to 600 μmol per liter]). The median time between the onset of symptoms and death was 32 days (IQR, 24 to 48). For the 21 cases with available information, the median liver weight at death was 600 grams, and 32 (89%) of the 36 cases with autopsy reports had histologic features of hepatic necrosis or acute yellow atrophy. In only 11 of the 43 cases (26%) with death certificates was isoniazid mentioned as a factor contributing to the death.

TABLE 4.—*Appropriateness of Isoniazid Preventive Therapy Among Combined Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Treatment Period	Appropriate Therapy, No.	Inappropriate Therapy, No.	Insufficient Data, No.
1970	1	0	0
1971-1973	3	0	15*
1974-1983	20	5	4
1984-1986	5	0	1
1987-1990	8	0	0

*In 13 cases, participants were from Maryland in the 1971-1973 US Public Health Service study, and data were not available concerning indications for isoniazid prophylaxis.

Appropriateness of Isoniazid Preventive Therapy

Six different sets of recommendations for isoniazid preventive therapy were in effect during the study period.[11-16] Table 4 shows the number of cases occurring in each of the five periods and the authors' judgment concerning the appropriateness of isoniazid preventive therapy according to the guidelines in effect at the time. All patients received appropriate doses of isoniazid. The four deaths in women who were pregnant when isoniazid therapy was started all occurred in the 1980s when the guidelines in effect recommended against starting isoniazid preventive therapy during pregnancy. One 38-year-old woman continued to receive isoniazid despite two negative tuberculin skin tests because she was a tuberculosis contact. Another woman had previously received medication for a year as a participant in a Public Health Service study in 1964—indicating that she may have been unnecessarily retreated with isoniazid in 1985 for a 20-mm tuberculin reaction. The 1964 medication, however, was not definitely identified in the medical records as isoniazid, so it was not possible to judge the appropriateness of the treatment that led to her death.

Discussion

In a large eastern European clinical trial,[9] isoniazid preventive therapy increased the risk of acute hepatitis by fivefold, and the rate of fatal isoniazid hepatitis was 14 per 100,000 person-years. Estimates of the risk of death from isoniazid hepatitis vary considerably, however, and are affected by the characteristics of the population studied and by the degree of clinical vigilance that patients receive while taking isoniazid. In the Public Health Service study of 1971 to 1973, the rate of fatal isoniazid hepatitis was 55 per 100,000 person-years,[8] but the unexpectedly large number of deaths may have been related to local environmental factors in Baltimore, Maryland.[35]

A lack of reliable denominator data has precluded making accurate estimates of the risk of fatal isoniazid hepatitis in the general population.[27] Snider and Caras, however, estimated that at least 1,084,760 persons began isoniazid preventive therapy in the United States during 1972 to 1988 and at least 655,867 completed therapy.[28]

Assuming that the 46 fatal cases treated in the public sector during 1972 to 1988 that we identified represented the totality of cases of fatal isoniazid hepatitis from that population, the estimated rate of fatal isoniazid hepatitis was no greater than 4.2 per 100,000 persons beginning therapy and no greater than 7 per 100,000 persons completing therapy. The estimated rates for 1984 to 1988—during which time routine monitoring of hepatic enzyme levels was recommended for persons older than 35 years of age—were 1.7 per 100,000 starting therapy and 2.9 per 100,000 completing therapy.

Although recent case series have emphasized the dangers of isoniazid preventive therapy,[22,23,36] decision analysis suggests that the benefits of isoniazid preventive therapy outweigh the risks,[36] particularly when considering the additional benefits of preventing the spread of infection to others.[35] But without accurate data concerning the risk of fatal hepatitis as a result of isoniazid preventive therapy, decision analyses should be interpreted with caution. Rose and colleagues, for example, assumed that the risk of death from isoniazid preventive therapy in persons younger than 35 years of age is nil, which is not supported by our data.

Among the 28 fatalities in cases from 15 to 50 years of age, only 5 were men. In the absence of good denominator data, this finding is difficult to interpret, but the high proportion of women in this age group among the cases suggests that women of childbearing age may be at higher risk than men for death from isoniazid hepatitis.

Of the cases, 26 (42%) were monitored monthly in accordance with current recommendations; 6 of these were younger than 35 years and thought to be at low risk for isoniazid hepatitis. Furthermore, 23 patients (38%) stopped taking isoniazid within a week of the development of symptoms of hepatitis, suggesting that a substantial proportion of cases had a fatal outcome despite appropriate monitoring. The relatively large proportion of deaths that occurred among those younger than 35 years is consistent with the findings of Snider and Caras.[28] The current guidelines, which do not advise routine monitoring of hepatic enzymes for those younger than 35 years,[17] may need to be reconsidered in light of the relatively large proportion of patients in this series who were young and who died despite stopping the medication soon after symptoms developed.

This case series is limited by incomplete case ascertainment. We have calculated fatality rates by dividing the number of cases treated in the public sector by the approximate number of persons who, according to Snider and Caras, received isoniazid preventive therapy in the public sector,[28] but these estimates should be interpreted with caution. Almost all the cases we identified had received their care in the public sector, which suggests that we may have failed to identify additional cases from the private sector. For example, during our search we were unaware of some of the recently reported cases associated with liver transplant units in New York.[24] Manufacturers of isoniazid have estimated that half of their sales are to private sources,[28] although the proportion used for preventive therapy is unknown. We were reminded many times while collecting the clinical data that the fear of litigation is common; health care professionals may be reluctant to attribute a patient's death to prescribed therapy. The obstacles to reporting iatrogenic illness are great, and we expect that we underestimated the actual number of deaths from isoniazid hepatitis. Furthermore, the cases we investigated had previously been subjected to sometimes rigorous scrutiny, suggesting that some actual cases may have been rejected by others on the basis of having other identified risk factors for hepatitis. Nonetheless, many of our health department contacts were emphatic that if a case had occurred, they would have known about it.

We attempted to collect data from each state regarding the total number of persons treated annually with isoniazid preventive therapy, and we were struck by the lack of organized systems for collecting such data. The United States has no coordinated system for reporting fatal reactions to isoniazid preventive treatment. The FDA has the responsibility for monitoring drug toxicity, but only 2 of the 20 deaths reported by Moulding and co-workers had been reported to the FDA before the authors' investigation.[22] Death certificates also appear to be an insensitive means of detecting cases. The burden of proof for the safety of preventive programs is high, and the comprehensive national immunization toxicity surveillance program could serve as a model for a similar program to monitor tuberculosis preventive therapy.

In summary, isoniazid preventive therapy poses a dilemma for physicians. Tuberculosis incidence rates are rising, isoniazid prevents active tuberculosis in infected persons, and no other drug can effectively replace isoniazid. A small proportion of patients experience serious hepatotoxicity from isoniazid, however. Adherence to isoniazid preventive therapy guidelines apparently reduces, but does not eliminate, the risk of fatal isoniazid-related hepatitis. Although the risk is low, careful patient selection, education, and monitoring are critical for minimizing that risk.

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REFERENCES

1. Ferebee SH, Mount FW: Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. Am Rev Respir Dis 1962; 85:490-510

2. Ferebee SH, Mount FW, Murray FJ, Livesay VT: A controlled trial of isoniazid prophylaxis in mental institutions. Am Rev Respir Dis 1963; 88:161-175

3. Comstock GW, Ferebee SH, Hammes LM: A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Respir Dis 1967; 95:935-943

4. Merrit AD, Fetter BF: Toxic hepatic necrosis (hepatitis) due to isoniazid: Report of a case with cirrhosis and death due to hemorrhage from esophageal varices. Ann Intern Med 1959; 50:804-810

5. Maddrey WC, Boitnott JK: Isoniazid hepatitis. Ann Intern Med 1973; 79: 1-12

6. Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR: Isoniazid-associated hepatitis in 114 patients. Gastroenterology 1975; 69:289-302

7. Garibaldi RA, Drusin RE, Ferebee SH, Gregg MD: Isoniazid-associated hepatitis—Report of an outbreak. Am Rev Respir Dis 1972; 106:357-365

8. Kopanoff DE, Snider DE Jr, Caras GJ: Isoniazid-related hepatitis: A US Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978; 117:991-1001

9. International Union Against Tuberculosis: Efficacy of various durations of isoniazid preventive therapy for tuberculosis: Five years of follow-up in the IUAT trial. Bull WHO 1982; 60:555-564

10. American Thoracic Society: Preventive treatment in tuberculosis—A statement by the committee on therapy. Am Rev Respir Dis 1965; 91:297-298

11. American Thoracic Society: Chemoprophylaxis for the prevention of tuberculosis. Am Rev Respir Dis 1967; 96:558-560

12. American Thoracic Society: Preventive treatment of tuberculosis. Am Rev Respir Dis 1971; 104:460-465

13. American Thoracic Society: Chemoprophylaxis for the prevention of tuberculosis—A statement by an ad hoc committee. Am Rev Respir Dis 1972; 106:357-365

14. American Thoracic Society: Preventive therapy of tuberculosis infection. Am Rev Respir Dis 1974; 110:311-314

15. American Thoracic Society: Treatment of tuberculosis and other mycobacterial diseases. Am Rev Respir Dis 1983; 127:790-796

16. American Thoracic Society: Treatment of tuberculosis and tuberculosis infection in adults and children. Am Rev Respir Dis 1986; 134:355-363

17. Centers for Disease Control and Prevention (CDC) Advisory Committee for the Elimination of Tuberculosis: The use of preventive therapy for tuberculous infection in the United States. MMWR 1990; 39(RR-8):9-12

18. CDC: A strategic plan for the elimination of tuberculosis in the United States. MMWR 1989; 38(suppl S-3):1-21

19. CDC: National action plan to combat multidrug-resistant tuberculosis. MMWR 1992; 41(RR-11):5-48

20. CDC: Update: tuberculosis elimination—United States. MMWR 1990; 39:153-156

21. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE: High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA 1992; 268:504-509

22. Moulding TS, Redeker AG, Kanel GC: Twenty isoniazid-related deaths in one state. Am Rev Respir Dis 1989; 140:700-705

23. Israel HL, Gottlieb JE, Maddrey WC: Perspective: Preventive isoniazid therapy and the liver. Chest 1992; 101:1298-1301

24. CDC: Severe isoniazid-associated hepatitis—New York, 1991-1993. MMWR 1993; 42:545-547

25. Tsevat J, Taylor WC, Wong JB, Pauker SG: Isoniazid for the tuberculin reactor: Take it or leave it. Am Rev Respir Dis 1988; 137:215-220

26. Moulding T, Barnes P: Isoniazid for the tuberculin reactor: Take it or leave it (Letter). Am Rev Respir Dis 1988; 138:488

27. Iseman MD, Miller B: If a tree falls in the middle of the forest. Am Rev Respir Dis 1989; 140:575-576

28. Snider DE Jr, Caras GJ: Isoniazid-associated hepatitis deaths: A review of available information. Am Rev Respir Dis 1992; 145:494-497

29. Salpeter SR: Fatal isoniazid-induced hepatitis—Its risk during chemoprophylaxis. West J Med 1993; 159:560-564

30. Levin ML, Moodie AS: Isoniazid prophylaxis and deaths in Baltimore, 1972. MD State Med J 1974; 23:64-67

31. Franks AL, Binkin NJ, Snider DE Jr, Rokaw WM, Becker S: Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 1989; 104:151-155

32. Gal AA, Klatt EC: Fatal isoniazid hepatitis in a child. Pediatr Infect Dis 1986; 5:490-491

33. Moulding TS, Redeker AG, Kanel GC: Acetaminophen, isoniazid, and hepatic toxicity (Letter). Ann Intern Med 1991; 114:431

34. Vanderhoof JA, Ament ME: Fatal hepatic necrosis due to isoniazid chemoprophylaxis in a 15 year-old girl. J Pediatr 1976; 88:867-868

35. Comstock GW: Prevention of tuberculosis among tuberculin reactors: Maximizing benefits, minimizing risks. JAMA 1986; 256:2729-2730

36. Rose DN, Schechter CB, Silver AL: The age threshold for isoniazid chemoprophylaxis—A decision analysis for low-risk tuberculin reactors. JAMA 1986; 256:2709-2713

Articles

Factors Associated With Choosing a Primary Care Career

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The factors influencing the career choices of medical students need to be understood so that the proportion of physicians entering primary care—defined as family practice, general internal medicine, general pediatrics, and general obstetrics and gynecology—can be increased. We sent a questionnaire to 474 University of California, San Diego (UCSD), School of Medicine alumni (classes of 1974, 1978, 1982, 1986, and 1990) inquiring about demographics, personal and medical school factors, and level of debt. A total of 351 alumni responded (74% response rate), and 327 of them were engaged in direct patient care (38% in primary care). Respondents who were older, female, an underrepresented minority, from a rural background, and who chose their specialty before medical school were significantly more likely to enter primary care. The primary care group was influenced by factors unrelated to the medical school environment, such as personal social values, whereas the top 3 factors rated by the non–primary care group were directly related to school environment. Many of the respondents in primary care reported that the environment at UCSD was antagonistic toward primary care. From 1974 to 1990, more students had debt and their total debt increased, although debt had little or no influence on specialty choice.

(Schieberl JL, Covell RM, Berry C, Anderson J: Factors associated with choosing a primary care career. West J Med 1996; 164:492-496)

In 1992 the Association of American Medical Colleges (AAMC) accepted the recommendations of its Generalist Physician Task Force to undertake activities to increase the number of general internists, pediatricians, and family practitioners in the workforce.[1,2] The Physician Payment Review Commission and the Council of Graduate Medical Education have also periodically issued statements on the need for more generalists, and this concern has been expressed in proposed federal legislation. Further, growing managed care markets are disproportionately hiring primary care physicians, and several states have legislated primary care training goals. The California Legislature passed bills in 1993 and 1994 (Assembly Bills 3593 and 1855, Isenberg) to increase training in primary care at the University of California's five medical schools. The governor vetoed the bills when the university formally pledged to increase the number of generalist residency positions and to decrease the number of specialty residency positions, as reported in "Changing Directions in Medical Education: A Systemwide Plan for Increasing the Training of Generalists," June 1993 (University of California, Office of the President, 1994) and subsequent updates. Given these national, economic, and state forces, it is increasingly important to better understand how medical students make specialty choices.

Many studies have been done of how medical students decide on a specialty. Some focused on the effects of student characteristics, public versus private funding of medical school, the presence and strength of family medicine departments, and whether the curriculum required exposure to primary care.[3,4] In one study, the class of 1985 admission data were examined for predictors of specialty choice.[5] Other investigators used alumni surveys, often in combination with university data, to determine predictive factors.[6-10] The AAMC started its own prospective tracking of career choices for each medical school in the early 1980s.[11]

California policy makers have defined the primary care specialties as family medicine, general internal medicine, general pediatrics, and general obstetrics and gynecology.[12] The last was due in part to issues of access to prenatal care. The Institute of Medicine defines primary care physicians as those who provide integrated, accessible health care services and who address a large majority of personal health care needs, develop a sustained partnership with patients, and practice within the context of the family and the community.[13]

No consistent picture has emerged of a student bound for primary care. Evidence of the effects of factors such as age, sex, ethnicity, and marital status is conflicting. The medical school environment is thought to have a critical effect on medical students' specialty choices,[3] although

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ABBREVIATIONS USED IN TEXT

AAMC = Association of American Medical Colleges
UCSD = University of California, San Diego

the influence of faculty and the presence of family medicine departments is unclear. Michigan medical students reported that faculty had little to do with their decisions,[14] whereas the General Accounting Office found that schools with departments and required clerkships in family medicine had more graduates who chose generalist careers.[4] A recent study found that admission criteria, curriculum design, and faculty role models are the most influential factors under medical schools' control.[3] That study reported personal social values as the strongest influencing factor on choosing primary care. Another study found that prestige and the desire for a large income correlated with choosing high-technology specialties.[8]

The University of California, San Diego (UCSD), School of Medicine is a publicly supported school in a large city and part of the University of California nine-campus system. The UCSD Medical Center cares for a large indigent population as well as private-pay patients—there is no county hospital in San Diego County—while serving as a cutting-edge research institution. The UCSD School of Medicine ranks well among United States medical schools for placing graduates into primary care—19th with the universities of South Dakota, North Carolina, and Arkansas. For the combined years 1988 through 1990, 32% of graduates entered primary care (not including obstetrics and gynecology).[15] State government intervention is causing all University of California medical schools to increase the production of primary care physicians. To inform this process, this study's goal is to better understand the influence of demographics, environment, and debt on medical students' decisions. It is important to note that due to the inclusion of obstetrics and gynecology in primary care, selected results of this study will not be fully comparable with studies that excluded that specialty.

Methods

The study sample consisted of 474 UCSD alumni from the classes of 1974, 1978, 1982, 1986, and 1990 (the charter class graduated in 1972). Most 1990 graduates who planned to subspecialize in medicine or pediatrics would have done so by the time of this study. The questionnaire was mailed in October 1994. A follow-up questionnaire was mailed six weeks later to the nonrespondents. A total of 351 completed questionnaires were received, for a 74% response rate. All responses were anonymous, and no other data were used. Confidentiality policies precluded access to identifiable UCSD data.

Demographic factors possibly affecting specialty choice were elicited. Hispanics, Latinos, blacks, and Native Americans are considered underrepresented minorities at UCSD. A student's place of origin was defined as the type of location where the respondent spent the most time before medical school.

Factors representing undergraduate medical experiences and personal values perceived as important in making a specialty choice were rated by respondents as follows: 0 = "no influence," 1 = "little influence," 2 = "moderate influence," and 3 = "strong influence." A mean score was generated for each response.

Respondents estimated their level of total debt at graduation, including all sources such as undergraduate debt. For analysis, debt was expressed in 1982 dollars per the Consumer Price Index.

Statistical analysis for the demographics consisted of Pearson's χ^2 test for homogeneity in the $r \times c$ table and Cochran's test for linear trend. Statistical analysis for the perceived factors was Cochran's test for linear trend comparing the primary care and non–primary care responses within each category of influence. The average debt was tested between groups with the two-sample t test. Cochran's test for linear trend was used to test for the influence of debt on choosing primary care medicine. The Pearson correlation was used to analyze the rise in aver-

TABLE 1.—*Demographic Characteristics Camparing Primary Care and Non–Primary Care Physicians*

Demographic Characteristics	*Respondents, No.*	*In Non–Primary Core, %*	*In Primary Care, %*	*P Value*
Overall	327	62	38	
Age at graduation (mean = 27.23), yr*				
24-25	46	65	35	
26	109	67	33	
27	71	59	41	
28-29	60	60	40	
30-36	39	54	46	<.05†
Sex				
Women	98	44	56	
Men	229	70	30	<.01‡
Marital status§				
Married	120	66	34	
Single	189	61	39	NS
Ethnicity‖				
White	249	65	35	
Asian/Pacific Islander	35	58	42	NS
Underrepresented minorities¶	40	47	53	<.05†
Place of origin				
Small town/rural	20	30	70	
Small city	79	52	48	
Suburb of large city	118	64	36	
Large city	110	75	25	<.001*
Point of decision				
Before medical school	32	25	75	
Preclinical years (MS I-II)		21	52	48
Clinical years (MS III-IV)	188	62	38	
Residency	86	79	21	<.001*

MS I-II = first- to second year medical student, MS III-IV = third- to fourth-year medical student, NS = not significant

*325 respondents reported their age at graduation.
†Cochran's test for a linear trend.
‡Pearson's χ^2 test in $r \times c$ table.
§309 respondents reported marital status.
‖324 respondents reported ethnicity.
¶Consists of Black, Latino, Hispanic, and Native American ethnicities.

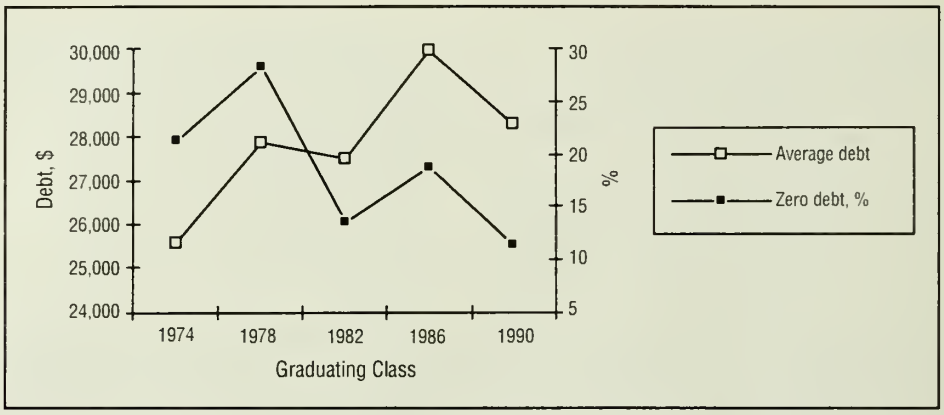

Figure 1.—The graph shows an increase in average debt for those who incurred debt and a decrease in the percentage of those with zero debt from the class of 1974 to 1990 (expressed in 1982 dollars).

age debt and the fall of the percentage with zero debt from 1974 to 1990. The Pearson χ^2 test for homogeneity in the $r \times c$ table was used to analyze percentage with zero debt between groups. A P value of less than .05 was considered significant when using a two-tailed test.

Results

In 327 (93%) completed questionnaires, a clinical specialty with the respondents remaining in direct patient care was listed. The remaining 24 (7%) were not engaged in direct patient care and were excluded from specialty choice analyses but included in the analysis of the level of debt. Of the respondents, 123 (38%) were in primary care (Table 1). Of the primary care physicians, 38 were general internists (31%), 36 in family practice (29%), 30 in general pediatrics (24%), and 20 in obstetrics and gynecology (16%). The breakdown of respondents in primary care by class is as follows: 1974, 52%; 1978, 32%; 1982, 36%; 1986, 45%; and 1990, 34%. The 204 respondents in the remaining specialty groups were distributed as follows: internal medicine subspecialties, 10%; pediatric subspecialties, 3%; obstetric and gynecologic subspecialties, 1%; general surgery and surgical subspecialties, 12%; and the support specialties, 36%. Most of the last category were represented by psychiatry, emergency medicine, anesthesia, dermatology, neurology, and radiology. The level of debt at graduation was reported by 343 (98%).

An analysis of demographic factors determined the importance of each for the choice of primary care or non–primary care specialty (Table 1). Respondents who were older, female, an underrepresented minority, from a rural background, and who chose their specialty before medical school were significantly more likely to enter primary care. Women were more likely to choose primary care than were men in all of the primary care fields, with the greatest ratio in general internal medicine (19.4% women to 8.3% men). Marital status had no significant influence on specialty choice.

The data on perceived school-related and personal factors are shown in Table 2. The primary care group was influenced by factors unrelated to the medical school environment, whereas the top three factors rated by the non–primary care group were related to the school environment. For example, the primary care group's highest mean score was for "personal social values"; for the non–primary care group, it was "clinical rotations within your specialty." The difference between groups for the factors "clinical rotations within your specialty" and "UCSD faculty role models" was almost entirely due to the lack of influence of these factors in family practice.

From 1974 to 1990, the number of indebted students and the average indebtedness increased (Figure 1). In 1974 the average debt from all sources expressed in 1982

TABLE 2.—*Mean Scores of Perceived Personal and School-Related Factors of Primary Care and Non–Primary Care Physicians**

Perceived Factor	*Mean Score*		*P Value*
	Primary Care Physicians	*Non–Primary Care Physicians*	
Those that influence the primary care group			
Personal social values	2.25	1.50	<.001
Desire for a broad scope of practice	2.02	1.08	<.001
Emphasis on patient education and prevention	1.81	0.85	<.001
Other physician role models	1.62	1.46	NS
Those that influence the non–primary care group			
Clinical rotations within your specialty	2.12	2.30	<.05
UCSD faculty role models	1.41	1.84	<.01
Electives	1.35	1.70	<.01
Lifestyle available in specialty	1.20	1.69	<.01
Emphasis on performing procedures	0.76	1.49	<.001
Desire for a narrow scope of practice	0.48	1.27	<.001
Hours/length of residency	0.95	1.14	<.05
Opportunity for research	0.41	1.06	<.001
Income potential	0.52	0.94	<.001
Independent study project	0.52	0.79	<.05
Prestige within the medical profession	0.56	0.78	<.01
Level of debt	0.18	0.29	<.05

NS = not significant, UCSD = University of California, San Diego

*The scores were arrived at by the following ratings: 0 = no influence, 1 = little influence, 2 = moderate influence, and 3 = strong influence.

dollars was $25,590. It increased to $28,310 by 1990 ($r$ = .76, P < .05). The percentage of students graduating with zero debt declined from 21% in 1974 to 11% in 1990 (r = –.69, P < .05). There was no significant difference between the primary care and the non–primary care groups when the level of debt or the percentage with zero debt was analyzed. No trend was found as the level of debt increased to suggest a move away from primary care.

Discussion and Conclusions

We found no temporal trend for the percentage of respondents entering primary care, although the class of 1974 had a greater proportion of graduates who entered primary care. The proportion of respondents in primary care in the 1986 and 1990 classes is similar to AAMC tracking data for UCSD.[11]

Many of the demographic factors were positively associated with choosing primary care. Respondents who were older than the mean at graduation were more likely to become generalists. The oldest group, older than 30 years, had the greatest proportion who chose primary care but was the smallest in number. Similar to the findings of another study, we found that women entered primary care in significantly greater numbers than did men.[10] In the previous study, the higher proportion of women in primary care was due to their greater numbers in general pediatrics and obstetrics and gynecology, not in general internal medicine. Women alumni of UCSD were also disproportionately represented in general pediatrics and obstetrics and gynecology; however, the most significant difference was in general internal medicine. No significant gender difference was found in family practice. Female students could have the greatest influence on increasing the number of graduates in primary care because women are approaching 50% of enrollment at UCSD and elsewhere.

Earlier studies are in conflict regarding the specialty preference of minority students.[3,4,8] We found that underrepresented minority graduates chose primary care significantly more frequently than did white respondents. A higher percentage of Asian respondents than white respondents entered primary care, but the difference was not significant. Among the small number of respondents who decided their specialty before entering medical school, 75% chose primary care. Most made career decisions in their third or fourth year, which did not favor or disfavor primary care. These data may not be useful in the admission process because many applicants may declare a preference for primary care once it is known to influence admissions, but the use of corroborating evidence, such as premedical extracurricular activities, might be helpful. As expressed elsewhere,[15] the latter two years of medical school should be the primary target for change because most decisions are made then. The respondents who spent most of their time before medical school in a small town or rural environment (6%) chose primary care 70% of the time. This was nearly threefold more than those from a large city. Of those from a small city, 48% chose primary care, nearly a twofold increase over those from a large city.

The influence of personal factors was perceived differently between the primary care group and the non–primary care group (Table 2). The influencing factors that favored the primary care group were all personal. As noted by others, personal social values were the strongest influencing factor for the primary care group.[3] Therefore, the detection of these personal attributes could be used to affect admission policies. As expected, the primary care group favored a broad scope of practice, with an emphasis on patient education and prevention. The primary care group also had a higher mean score for the factor "other physician role models," but it was not significant.

Other personal factors favored the non–primary care group, such as the significantly stronger influence of hours worked and length of residency training. This could be related to the fact that primary care residencies are distinctively shorter (obstetrics and gynecology excluded) than the non–primary care specialties. As expected, the non–primary care group strongly favored a narrow scope of practice, with an emphasis on doing procedures. The lifestyle available in one's specialty had a strong influence on the non–primary care group. A further breakdown revealed that those who chose family practice rated it as an even stronger influence than the non–primary care group. It is unclear how to interpret the results because lifestyle could mean many different things. For example, lifestyle could be related to income for some physicians and amount of personal time for others. The greater influence of income potential on the non–primary care group was expected. This reflects the difference in earning potential between the groups, with non–primary care specialists earning significantly more than primary care specialists (excluding obstetrics and gynecology). Although there was a statistically significant difference in scores, the level of debt as a perceived factor had minimal to no influence on either group.

The medical school environment had a greater influence on the non–primary care group. The UCSD faculty had a strong effect on specialty choice for the non–primary care group. A further breakdown revealed that the difference was largely due to the low response of those entering family practice. This is despite the fact that UCSD has a large, well-established family practice program and a growing department within the past decade. Clinical rotations within their specialty was the strongest influencing factor for the non–primary care group. Further analysis showed that nearly the entire difference between groups is due to a lack of influence on those in family practice. Family practice was the only primary care specialty that did not have any core time in the third-year curriculum, suggesting that the medical school environment promotes or disfavors primary care through clinical exposure. As expected, the non–primary care group was significantly more influenced by the prestige associated with their specialty. At UCSD, non–primary care specialty and subspecialty physicians dominate, an imbalance that the university has recently addressed by increasing exposure to primary care faculty.

Literature reports have shown that primary care physicians do much less clinical research than their non–

primary care colleagues.[7,10] This study supports those results, raising the concern of exacerbating the declining interest in research by medical graduates by shifting physicians into primary care. Promoting primary care research and exposing those students interested in primary care to clinical research could help, although further study is necessary.

As expected given previous studies reporting that debt greater than $75,000 is required to affect students' specialty choices, there was little influence of debt on UCSD graduates.[16] This may be a problem in the future if tuition or fee increases continue, coupled with more economically diverse student bodies. The findings suggest that there is a debt threshold at which UCSD students will become increasingly sensitive to their potential income and corresponding specialty choice. It is important to note that we asked for debt from all sources because medical school debt is not a complete marker, and it is total debt that may influence specialty choice.

General comments were solicited in the questionnaire and were often directed at the perceived hostility toward primary care (especially family medicine) at UCSD. "UCSD was an unfriendly school for family practice . . ." commented a 1982 graduate, and "I did find the bulk of UCSD faculty very antagonistic towards primary care," said a 1990 graduate. Many of these same alumni had a faculty member or resident who inspired them: "I was miserable, but I had a great resident who encouraged me," said a 1982 graduate. "My number 1 reason for choosing my specialty was one UCSD faculty role model practicing prevention, patient education, and whole patient care," said a 1990 graduate. These comments show that support for primary care within the medical school was critical in attracting students.

Comments from subspecialists displayed critical variations in personality and personal characteristics: "My interest in dermatology came from personal skin problems prior to medical school." "A chance to cut is a chance to cure." "Plastic surgery is creative, artistic, and problem solving." "I strongly disliked patients with long medical histories and big charts."

Two consistent themes permeate the results. First, certain demographic factors were strong indicators for choosing primary care. Although it may be difficult to select for characteristics such as sex, ethnicity, and place of origin, personal social values could be selected for or influenced. Second, the environment has a strong influence on graduates' specialty choices, regrettably often a negative effect on primary care specialties (especially family practice). The university is changing its environment to increase primary care exposure. The class of 1995 was the first to have a required fourth-year primary care rotation. A required primary care longitudinal experience of half a day per week throughout the third year has been implemented for the class of 1997. The only required primary care experience for the alumni surveyed was a four-week outpatient pediatrics rotation in the third year, although they had fourth-year elective time to pursue other primary care opportunities. Changes in graduate medical education at UCSD include increasing primary care residency slots while decreasing others and creating a new, affiliated, community-based family practice residency. In fact, UCSD's environment is changing rapidly because it must not only comply with state mandates but adjust to perceived workforce requirements of the next several decades. Further follow-up studies will be needed to test the response of students to these changes in curriculum and practice environment. Indeed, the latter may be a major factor for students entering specialty training in the 1990s. Primary care fields are the initial specialty choice of 61% of the class of 1995, 53.5% if obstetrics and gynecology is excluded.

REFERENCES

1. AAMC Generalist Physician Task Force: Association of American Medical Colleges Policy on the Generalist Physician. Acad Med 1993; 68:1-6

2. Greer DS, Bhak KN, Zenker BM: Comments on the AAMC policy statement recommending strategies for increasing the production of generalist physicians. Acad Med 1994; 69:245-260

3. Martini CJ, Veloski JJ, Barzansky B, Xu G, Fields SK: Medical school and student characteristics that influence choosing a generalist career. JAMA 1994; 272:661-668

4. Medical Education: Curriculum and Financial Strategies Needed to Encourage Primary Care Training: A Report of the General Accounting Office, publication No. HEHS-95-9, 1994

5. Madison DL: Medical school admission and generalist physicians: A study of the class of 1985. Acad Med 1994; 69:825-831

6. Greer T, Carline JD: Specialty choice by medical students: Recent graduate follow-up survey at the University of Washington. Fam Med 1989; 21:127-131

7. Rogers LQ, Fincher RM, Lewis LA, Nance LD 3d: A survey to determine factors influencing medical students' career choices. Acad Med 1989; 64:417

8. Kassler WJ, Wartman SA, Silliman RA: Why medical students choose primary care careers. Acad Med 1991; 66:41-43

9. Kassebaum DG, Szenas PL: Factors influencing the specialty choices of 1993 medical school graduates. Acad Med 1994; 69:164-170 [erratum published in Acad Med 1994; 69:290]

10. Hojat M, Gonnella JS, Erdmann JB, Veloski JJ, Xu G: Primary care and non-primary care physicians: A longitudinal study of their similarities, differences, and correlates before, during, and after medical school. Acad Med 1995; 70: S17-S28

11. University of California, San Diego, School of Medicine GME Activity of Recent Graduates through 1993-1994 Residency Year: A Report. Washington, DC, Association of American Medical Colleges, 1994

12. Cal Welfare Inst Code: Pub Soc Serv §14254; 400

13. Donaldson M, Yordy K, Vanselow N (Eds): Defining Primary Care: An Interim Report, Part 3—The New Definition and an Explanation of Terms. Washington, DC, National Academy Press, 1994 pp 15-16

14. Gorenflo DW, Ruffin MT, Sheets KJ: A multivariate model for specialty preference by medical students. J Fam Pract 1994; 39:570-576

15. Meurer L: Influence of medical school curriculum on primary care specialty choice: Analysis and synthesis of the literature. Acad Med 1995; 70:388-397

16. Kassebaum DG, Szenas PL: Relationship between indebtedness and the specialty choices of graduating medical students: 1993 Update. Acad Med 1993; 68:934-937

Articles

Centennial of Röntgen's Discovery of X-rays

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November 8, 1995, marked the 100th anniversary of Wilhelm Conrad Röntgen's discovery of x-rays. This remarkable scientific achievement has had an effect on medicine and science that has been matched by few other advances. I will briefly review the events leading up to Röntgen's discovery and the subsequent development of radiology as a discipline.

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November 1995 marked the centennial of one of the great discoveries of science. On November 8, 1895, Wilhelm Conrad Röntgen (1845 to 1923) discovered a mysterious new ray that he later called the "x-ray," signifying the unknown and puzzling nature of this type of radiation or perhaps his own modesty.[1] This name has, of course, remained in use for the intervening century, although some still refer to x-rays as "roentgen rays," a term that was used by others shortly after Röntgen's discovery in recognition of his great achievement. In view of the pivotal role of this discovery in the development of many aspects of medical science, including diagnosis, treatment, epidemiology, public health, and pathophysiology, it is appropriate to commemorate Röntgen's seminal work with a brief review.

Röntgen was born in Lennep in what is now the Rhineland region of Germany in 1845. His parents were first cousins.[2] His mother's ancestors were from Holland, and the Röntgen family moved to Apeldoorn, Holland (now the Netherlands), when Wilhelm was 3 years of age. His father was a merchant. Because of the move, the family lost their Prussian citizenship and became Dutch citizens in 1848, the year of their move.[3]

An average student in primary and secondary school, Röntgen entered the Utrecht Technical School in Holland in 1862. Completion of that curriculum would have prepared him only to enter a technical high school; he would not have qualified for entry into a university. He did not complete the curriculum, however, being expelled because he refused to name a fellow student who had mocked the teacher in class.[3] After auditing mostly science courses at the University of Utrecht, Röntgen moved to Zürich, Switzerland, in November 1865 to enroll as a student of mechanical engineering at the federal Polytechnical School, graduating as a mechanical engineer in 1868.[4] His only physics course there was one semester in technical physics taught by R. J. E. Claussius (1822 to 1888), a German mathematical physicist who is regarded as the father of thermodynamics and who is honored by having one of the moon's craters named after him. There is no evidence, however, that Claussius had any specific influence on the direction of Röntgen's career.

After graduation, Röntgen remained in Zürich as a graduate student in mathematics at the University of Zürich. His mentor was August Kundt, an authority in the theory of light. Röntgen's first experiments at Zürich concerned the properties of gases and proved to be important in his subsequent discoveries. His doctoral thesis, *Studien über Gase* ("Studies on Gases"), led to his being awarded the PhD degree in 1869 and also led to his appointment as assistant to Kundt. Röntgen returned to his native Germany in 1870 when he followed Kundt to the University of Würzburg in Bavaria. He again followed his mentor in 1872 when Kundt was appointed to the chair of the department of physics at the Kaiser Wilhelms University in Strassburg. Röntgen's initial faculty appointment came at that same institution in 1874.

Over the next five years, Röntgen had appointments as professor in physics and mathematics in Hohenheim and associate professor in theoretical physics at Strassburg. His experimental work during this time included various studies of gases and also measurements of the discharges of electricity through conductors.

Cathode rays had been discovered by Geissler and others in the 1850s.[5] These rays consist of electrical current that is emitted from the cathode end of a vacuum tube when a high-tension electrical discharge is passed through it, and their discovery came because of the fluorescence produced when the rays struck fluorescing materials. Such a tube had been developed in 1869 by Hittorf and later modified in 1879 by Crookes by altering the shape.[6] These tubes had relatively thick glass walls. As the vacuum increased, the passage of current decreased until it would not pass through the tube. The most important experiments with cathode rays were conducted by Philipp Lenard, Director of the Physical Institute at Heidelberg University. In 1892 Lenard constructed a glass vacuum tube containing a window and covered this window with a thin layer of aluminum. He demonstrated that the cathode rays passed through the aluminum to the out-

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side, made the air outside the tube electrically conductive, were absorbed in the first few centimeters of air, caused luminescence of certain fluorescent salts, and darkened a photographic plate.[3] Röntgen repeated some experiments regarding the effects of cathode rays on air and hydrogen and was so stimulated by this work that he dropped his other research and worked exclusively on cathode rays.

In his critical series of experiments, Röntgen completely covered a Lenard tube with cardboard and foil to prevent any visible light from escaping from the tube. He directed the cathode rays toward a small screen coated with barium platinocyanide, a fluorescent material. He confirmed that the cathode rays caused fluorescence if the coated screen was placed close to the window of the tube. Knowing that Hittorf and Crookes tubes produced light when current was passed through them, he postulated that they might also produce cathode rays that caused fluorescence, but that this fluorescence might be obscured by the luminescence. He therefore completely covered a Crookes tube with cardboard and showed that no light passed through the cover when current was passed through the tube. Just before he moved to the next phase, when he planned to set up a barium platinocyanide-coated screen to look for cathode ray fluorescence, he happened to note a faint green light shimmering on a nearby bench. (The actual color perceived by Röntgen is of some interest because he was color blind![2]) He confirmed this observation on repeating the experiment and noted that the intensity of the green color fluctuated along with the fluctuating electric current. He discovered that the light was coming from the barium platinocyanide-coated screen that was lying on the bench and was to have been used for the next experiment. He showed that the fluorescence was produced even when the screen was at some distance from the tube, thus proving that something other than cathode rays was responsible for the fluorescence.

That Friday, November 8, 1895, and over the ensuing weekend, Röntgen repeated and expanded his work and documented his activities. He demonstrated that these rays could penetrate not only glass and air but a variety of materials, including various metals. He demonstrated that a thin sheet of lead completely blocked them. He also inferred that they were in fact rays because they traveled in straight lines and created shadows of the type that would be created by rays. While studying the ability of lead to stop the rays, Röntgen held a small piece of lead between his thumb and index finger and placed it in the path of the rays. He noted that he could distinguish the outline of the two digits on the screen and that the bones appeared as darker shadows than did the surrounding soft tissue. This was the first x-ray image of a part of the human body. Thus, an amazing amount of the foundation of clinical radiology was established that first weekend!

Röntgen continued his work over the next several weeks, during which he made additional images and showed that the rays darkened a photographic plate. Finally, he submitted his manuscript, *Über eine neue Art von Strahlen* ("On a New Kind of Rays") to the Physikalisch-Medizinische Gesellschaft in Würzburg on December 28, 1895.[7] In this paper he used the term "x-rays" for the first time. The first published account of his work appeared in *The Presse* of Vienna on January 5, 1896. *The Presse* noted, regarding the demonstration of bones,

> The surgeon could then determine the extent of a complicated bone fracture without the manual examination which is so painful to the patient: he could find the position of a foreign body such as a bullet or a piece of shell much more easily than has been possible heretofore and without any painful examinations with a probe.[2(p455)]

Once Röntgen presented his work in Würzburg, word of his achievement spread rapidly. This rapid spread was accompanied by an almost immediate appreciation of some of the possible uses of his rays, as well as almost immediate application in a variety of situations.

The day after Röntgen's announcement, Dr J. R. Ratcliffe in Birmingham, England, produced a radiograph of his hand after he had pushed a sterilized needle under the skin of his palm. The film, of course, demonstrated the location of the needle. The following night, a woman came to Queen's Hospital in Birmingham with a needle embedded in her hand. Ratcliffe and colleague Hall-Edwards made a radiographic image of her hand and developed a bromide print of the radiograph. They gave the print to the patient, who took it to her surgeon the next morning. The surgeon used the photograph as a guide in removing the needle. This was presumably the first operation to be done based on the results of diagnostic x-ray images.[2]

Radiographic images were being produced in several sites in Germany in January 1896, the same month that Röntgen's discovery was announced. Electronic communications resulted in a rapid transmission of the news to the United States as well. American newspapers published the news of Röntgen's discovery as early as January 9, 1896.[7] By the third week of January, a New York newspaper reported that x-ray images had been used in Europe to locate foreign objects and diagnose diseases of bone.[8] Although it has been reported that x-ray photographs were being produced in this country in January 1896,[9] the first documented diagnostic x-ray photograph in the United States may be one obtained in the physics department of Dartmouth College, Hanover, New Hampshire, on February 3, 1896. This film of the left wrist of a 14-year-old boy who fell while ice skating showed an ulnar fracture.[9]

Radiology developed rapidly as a medical and scientific discipline. In 1896 x-ray images were used to demonstrate a wide variety of skeletal abnormalities and foreign bodies. The British are credited with the initial use of radiographs in treating those wounded in battle that same year. Images of various organs, the fetus in utero, and the calcification of tissues were also produced.[2]

Röntgen had noted the difficulties in using x-ray images for the diagnosis of abnormalities involving tissues other than bone. To overcome this limitation, in February 1896 blood vessels were injected after death with a mixture of lime, cinnabar, and petroleum to demonstrate vascular anatomy.[3] The following year in Boston, Massa-

chusetts, swallowed bismuth subnitrate was used to study the gastrointestinal tract of animals, and this technique was used in humans in 1898.[10]

Technical developments in 1896 included the use of fluoroscopy and cineradiography. Applications included submitting x-ray images as evidence in medicolegal cases, quality control in manufacturing metal products, detecting fraudulent documents and paintings, and inspecting postal parcels, all introduced in that same year.[2]

The widespread clinical use of x-rays was facilitated by scientific investigation and industrial application shortly after Röntgen reported his findings. Thomas Edison, who had invented the electric light bulb in the 1880s, began research on x-rays at his Edison Lamp Works in 1896. Among his studies were investigations of the source of x-rays, the tube to focus the rays, and the chemical substances that fluoresced when struck by x-rays. These last studies were important in the development of the Edison fluorescent lamp.[11]

A major advance occurred in 1913 at General Electric. The Crookes tube that Röntgen had used had been filled with gas, resulting in an erratic output of x-rays. Coolidge at General Electric used a cathode vacuum tube that produced a stable emission of x-rays. Later he introduced a tungsten alloy for both the cathode and the anode, and tungsten has been used for this ever since.[12] Interestingly, Edison had used calcium tungstate in his experiments, coating the inner walls of a vacuum tube into which x-rays were introduced. He envisioned a new type of lamp, but abandoned his research because of the adverse effects that resulted (described later).[11]

In addition to the development of better sources of x-rays, several other advances in the first few decades of radiology were crucial in facilitating the broad application of this diagnostic technique. Up to the 1920s, the x-ray-sensitive material was coated onto a glass plate. In the 1920s, the glass plate was replaced by celluloid film. Each piece of film contained a single x-ray image, and the film had to be changed after each picture was taken. The celluloid film was replaced with acetate, but this was a minor improvement in comparison to the next change. In 1931 the process was changed so that the x-ray-sensitive emulsion was applied to paper rather than film (R. J. Anderson, "In Search of TB Cases," *American Lung Association Bulletin*, March 1982, pp 11-13). In addition, multiple images could be applied to a single piece of paper as improvements in cameras and x-ray machines allowed for smaller images in some situations. These developments greatly reduced the time consumed in taking an x-ray image and reduced the cost from between $5 and $15 per picture to between 50 cents and a dollar. While these other technical advances were under way, there was also interest in reducing the time of exposure necessary for producing clinical radiographic images. This interest was driven partly by the practical need to be more efficient in processing patients. Early films required 15 minutes of exposure to x-rays to demonstrate the coarse structure of the bones of the hand. Thicker bones required longer exposures, so that a skull film might require an hour or more of exposure with the tube only 5 cm (2 in) from the head.[2] As discussed later, the recognition of toxic effects of exposure to x-rays also mandated attempts to reduce radiation exposure.

The development of intensifying screens was critical in reducing the amount of radiation necessary for the production of clinical radiographs. These screens (as currently used) are placed on each side of the x-ray film, forming a sandwich. The intensifying screen contains a fluorescent substance that produces fluorescent light when struck by x-rays, thus converting radiant energy to light energy. The x-ray film itself is extremely sensitive to light energy and reacts to the light produced by the intensifying screens, resulting in the final image. The use of intensifying screens reduces the amount of radiation necessary for the production of a clinical radiograph by a factor of $1/15$ to $1/30$ of that which would be necessary if there were no intensification.[12] This proved to be important in minimizing toxicity, in reducing the time necessary to make a diagnostic image, and in improving quality by reducing the motion of patients.

Tuberculosis was a leading cause of death in the United States in the latter part of the 19th century and remained one of the leading causes of death during the first few decades of this century, with a national death rate of 113 per 100,000 per year in 1920.[13] The rapid development of diagnostic radiology was widely applied to tuberculosis and proved to be critically important in the early detection of disease and the early institution of isolation. In the early years, there was debate about the relative merits of fluoroscopy and radiography in the diagnosis of tuberculosis, the former being less expensive, more rapid, and easier to interpret.[14] The technical developments outlined earlier led to the adoption of radiography rather than fluoroscopy as the major imaging technique for tuberculosis. Fluoroscopy, however, claimed an important role with the introduction of collapse therapy, that is, the creation of a therapeutic pneumothorax.[14]

The increased efficiency of making images and the decreased cost allowed the application of x-ray images to tuberculosis screening programs, and mass x-ray screening became the primary tool for tuberculosis control programs and remained so until the incidence of tuberculosis decreased sufficiently for the tuberculin skin test to be useful. The extent to which x-ray images were implemented is shown by the fact that in 1946, 6 million screening x-ray films were taken by public health screening programs in the United States. By 1950 the number had increased to 15 million.[15] With the development of antimicrobial therapy for tuberculosis treatment and subsequently for treating tuberculosis infection and preventing disease, radiography took on yet another crucial role in tuberculosis control.

Although the decrease in the tuberculosis incidence led to the elimination of mass screening for tuberculosis, diagnostic radiology continued to grow at a rapid pace after 1950, a pace that has not slowed yet. An estimated 260 to 330 million radiologic procedures were done in the United States in 1990. This is an average of 1.0 to 1.3 ra-

diologic procedures per citizen per year. The estimated cost was $19 to $22 billion, representing about 3.5% of the total national spending on health care.[16] At the Massachusetts General Hospital Medical Center alone, in 1992 there was a staff of 69 full-time practicing radiologists with a case load of more than 400,000 cases per year.[17] New developments continue, as does the rapid growth in the application of these new developments. Magnetic resonance (MR) imaging was first used clinically in 1982. Before October 1984, there were 72 MR units operational in the United States, and in 1990, 70 of these units were still operational. (There were, of course, many new MR units by that time.) In 1990, each of these 70 units performed an average of more than 3,000 examinations per year, for a total of 210,000 procedures from these 70 oldest units alone.[18]

The toxicity of x-rays became apparent soon after Röntgen discovered them. Hair loss was noted first, being recognized by May 1896. Skin toxicity was noted a few months later. Early x-ray images required exposures of as long as 80 minutes, and thus early x-ray workers were among the most severely affected. Dr Hall-Edwards, the British physician responsible for the first clinical x-ray photograph in England in early 1896, developed cancer of the hands from radiation exposure incurred while holding patients' extremities on photographic plates. In 1896, a commercial demonstrator at Bloomingdale Brothers store in New York, whose x-ray machine ran continuously for two to three hours a day, reported the development of dry skin, followed by changes similar to a strong sunburn and later scaliness of the skin. He also noted the cessation of fingernail growth and loss of hair from involved portions of the skin.[3] That same year Sir Joseph Lister postulated that

> the transmission of the rays through the human body may be not altogether a matter of indifference to internal organs, but may by long continued action produce, according to the condition of the part concerned, injurious irritation or salutary stimulation.[3(p91)]

Because of the erratic output of x-rays from the old gas-evacuated tubes, early radiologists had to examine their own hands with a fluoroscope to measure the output and gauge the needed exposure time for clinical radiographs.[17] Cancer of the skin of the hands was a major occupational health hazard for these early pioneers.[2]

Toxicity played a major role in Edison's decision to abandon his development of a new lamp using x-rays.[19] His assistant Clarence Dally suffered hair loss and skin ulcers. He had periodic acute inflammation of his left hand, with which he held the objects in the x-ray beam. Carcinoma of both of his hands developed, leading to bilateral amputation of the arms, and he died in 1904 of recurrent carcinoma.[11] Walter James Dodd, the first skiagrapher (equivalent to today's radiologist) at the Massachusetts General Hospital, died in 1916 of radiation exposure and a series of surgical procedures resulting from that exposure.[17]

Ironically, Röntgen had conducted virtually all of his experiments in a zinc box, which gave better definition of the x-ray beam. He had also added a lead plate to the zinc and thus fortuitously protected himself from the radiation that he discovered.[3]

The therapeutic use of x-rays was initiated shortly after Röntgen's discovery. The first reported case, a patient with carcinoma of the breast, was treated in 1896.[20] An increased therapeutic use of x-rays followed the observation of the destructive effects of x-rays on normal tissues. Unstandardized x-ray treatments were used in the first part of the 20th century. The first treatments using quantitated and qualitated doses of radiation were based on studies from the Frauenklinik (Women's Clinic) at Freiburg University in Germany. These studies were published in 1918.[3]

The French scientist Henri Poincaré postulated that because x-rays cause fluorescence, fluorescent substances might generate x-rays. His countryman, Henri Becquerel, confirmed that uranium produced similar rays, that is, gamma rays. Two other scientists working in France, Marie and Pierre Curie, identified other radioactive substances, among them radium,[21] which they discovered in 1896, and published their report in 1898.[22]

As noted earlier, the first standardization of x-ray therapy was at Freiburg. The pioneering studies of therapy using gamma rays from radium were carried out in the same institution.[3] Over the ensuing decades, there has been progressively greater usage of radiation therapy. In 1990, nearly 500,000 patients in this country were treated with radiation therapy.[23] Röntgen's discovery also provided the scientific basis for diagnostic nuclear medicine, another discipline that has experienced dramatic growth.

Röntgen was a modest man who shunned publicity. As with many who make dramatic discoveries, he was also the subject of much criticism. There were a number of reasons for this. One was the fact that others, for example, Goodspeed in Philadelphia, Pennsylvania, and Crookes in England, had made accidental x-ray photographs in the course of their studies. Neither had appreciated the importance of nor sought to explain their findings.[24]

Lenard himself had also noted the effects of x-rays, without appreciating the importance of his observation. At first he had been helpful to and supportive of Röntgen. It appears that his attitude may have changed after he sent Röntgen a letter of congratulations in 1897, expecting a reply acknowledging his own contributions. He never received such a letter. With the passage of time, he became increasingly bitter.[6] This hostility may have hardened when Röntgen received the first Nobel prize for physics in 1901. Lenard himself received the Nobel prize for physics in 1905, and his Nobel lecture was critical of Röntgen. Lenard subsequently became one of the leading scientists of Nazi Germany and a staunch supporter of the Nazis. There was then political reason to downplay the role of Röntgen and to advance the case for Lenard as the one who should receive credit for the discovery of x-rays.[6] Rumors had circulated shortly after Röntgen's discovery that the discovery had been accidental or that an assistant rather than Röntgen himself had made it.[24] Such rumors persisted after Röntgen's death and were advanced over the years by Lenard's supporters.

Röntgen was so embittered by the criticism and claims that he received credit for the work of others that he never published any material on x-rays after his initial three publications between 1895 and 1897.[8] Although he and others quickly recognized the importance of his discovery, no one could have anticipated the role of Röntgen's rays in medicine, science, and industry a century later. November 8, 1995, marked the 100th anniversary of a momentous discovery that bears recognition from all scientists.

REFERENCES

1. Gomez GE: Tribute to Wilhelm Conrad Röntgen. Am J Roentgenol Radiat Ther 1948; 60:96-103

2. Brailsford JF: Roentgen's discovery of x rays—Their application to medicine and surgery. Br J Radiol 1946; 19:453-461

3. Glasser O: Dr. W. C. Röntgen, 2nd edition. Springfield, Ill, Charles C. Thomas, 1958

4. Glasser O: Chronology of Röntgen's life. Am J Roentgenol Radiat Ther 1945; 54:541-552

5. Sante LR: Manual of Roentgenological Technique, 16th revised edition. Ann Arbor, Mich, Edwards Brothers, 1952

6. Etter LE: Some historical data relating to the discovery of the roentgen rays. Am J Roentgenol Radiat Ther 1946; 56:220-221

7. Hille H: From the memoirs of a student in Röntgen's laboratory in Würzburg half a century ago. Am J Roentgenol Radiat Ther 1946; 55:643-647

8. Spiegel PK: The first clinical x-ray made in America—100 years. AJR Am J Roentgenol 1995; 164:241-243

9. Glasser O: Early American roentgenograms. Am J Roentgenol Radiat Ther 1945; 54:590-594

10. Crandall DL, Barger A, Clifford HP: Bowditch's forgotten contributions to radiology. AJR Am J Roentgenol 1993; 161:1105-1108

11. Brown P: Clarence Madison Dally (1865-1904). AJR Am J Roentgenol 1995; 164:237-239

12. Thompson TT: Primer of Clinical Radiology. Boston, Mass, Little, Brown, 1980

13. Stead WW, Dutt AK: Epidemiology and host factors, chap 1, *In* Schlossberg D (Ed): Tuberculosis, 3rd edition. New York, NY, Springer-Verlag, 1993, pp 1-15

14. Keers RY: Pulmonary Tuberculosis—A Journey Down the Centuries. London, England, Baillière Tindall, 1978

15. Blakeslee AL: And the Spark Became a Flame. Queensboro, NY, Queensboro Tuberculosis and Health Association, National Tuberculosis Association, Brooklyn Tuberculosis and Health Association, Powers X-ray Products, Inc, 1954

16. Sunshine JH, Mabry MR, Bansal S: The volume and cost of radiologic services in the United States in 1990. AJR Am J Roentgenol 1991; 157:609-613

17. Wyman SM: Department of Radiology, Massachusetts General Hospital: A brief history. AJR Am J Roentgenol 1993; 160:1141-1144

18. Evens RG, Evens RG Jr: Analysis of economics and use of MR imaging units in the United States in 1990. AJR Am J Roentgenol 1991; 157:603-607

19. Cullinan J, Cullinan A: Early fluoroscopic imaging. Radiol Technol 1994; 66:119-124

20. Brady LW: Gold Medal Address: The Radiation Therapy Oncology Group—1987. Int J Radiat Oncol Biol Phys 1988; 15:537-542

21. Miller WT: Introduction to Clinical Radiology. New York, NY, Macmillan, 1982

22. Curie P, Curie Mme P, Bemont G: Sur une nouvelle substance fortement radioactive contenue dans la pechblende. Compt Rand Acad Sce (Paris) 1898; 127:1212-1217

23. Owen JB, Coia LR, Hanks GE: Recent patterns of growth in radiation therapy facilities in the United States: A patterns of care study report. Int J Radiat Oncol Biol Phys 1992; 24:983-986

24. Glasser O: Strange repercussions of Röntgen's discovery of the x-rays. Radiology 1945; 45:425-427

Conferences and Reviews

Magnetic Resonance Imaging of Multiple Sclerosis Lesions
Measuring Outcome in Treatment Trials

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Magnetic resonance-based measures of disease activity and progression are now routinely used in definitive phase III treatment trials of multiple sclerosis as important secondary outcome measures because they provide quantitative and objective confirmation of the primary clinical outcome measures. Magnetic resonance-based activity measures can also be used as an efficient mechanism for screening therapies in phase I and II trials. In this review I consider the natural history of multiple sclerosis lesions and the relationships between magnetic resonance measures and clinical observations of disease as the basis for the use of magnetic resonance markers in current and future treatment trials.

(Simon JH: Magnetic resonance imaging of multiple sclerosis lesions—Measuring outcome in treatment trials. West J Med 1996; 164:502-509)

Multiple sclerosis is a common cause of disability in young people, with the age of onset typically between 18 and 35 years. The prevalence of multiple sclerosis in high-risk areas, including the northern half of the United States, southern Canada, and central and northern Europe, ranges from about 30 to 200 per 100,000 population, and the incidence is about 3 per 100,000.[1] It has been estimated that five years after its onset, 30% of patients with the disease are unable to walk and conduct normal work activities, this disability increasing to 50% after ten years.[2]

Although until recently treatment was predominantly supportive (such as high-dose corticosteroid therapy) and resulted in only modest and transient benefit, a new optimism has developed since the introduction of the new generation of immunomodulatory therapies, including the interferons beta (IFN-β)[3-6] and other promising therapies.[6] A major obstacle in testing new therapies for multiple sclerosis is the limitations of the usual primary clinical outcome measures,[7] principally the progression of clinical disability, the relapse frequency, and the interval to relapse. Magnetic resonance (MR)-based measures of multiple sclerosis activity have been increasingly accepted as surrogate markers of disease.* The documented effects of high-dose therapy on the accumulation of brain lesions were important factors in the recent approval by the Food and Drug Administration of recombinant IFN-β1b,[8] and MR imaging outcome measures are currently a major component of nearly all the ongoing major United States and European multiple sclerosis treatment trials.†

*The term "surrogate markers" can be defined in two ways—that is, as nonclinical tests that could be used in place of clinical measures of disease or as a nonclinical test that may predict clinical change in a long-term disease.[7]

†See also the editorial by L. Jacobs, MD, "Magnetic Resonance Imaging in Clinical Therapeutic Trials of Multiple Sclerosis," on pages 531-532 of this issue.

Magnetic resonance imaging has become well established since its introduction in the early 1980s as the primary imaging approach in the clinical evaluation of multiple sclerosis. The clinical role of MR imaging is based on its sensitivity to the macroscopic pathologic processes in the brain and spinal cord, and MR imaging clearly depicts the anatomic distribution of lesions, improves confidence in the diagnosis, and expedites the diagnosis of this disorder.[9] The MR-based measures used in multiple sclerosis studies and their importance as outcome measures in treatment trials are the subject of this review.

Nature and Natural History of Magnetic Resonance Imaging–Detected Multiple Sclerosis Lesions

The primary factor responsible for the conspicuity of a lesion in the brain or spinal cord by conventional nonenhanced MR imaging is a nonspecific focal disturbance of the water environment. This causes a small increase in the concentration or proton density of water and larger changes (increases) in the longitudinal (T1) and transverse (T2) relaxation times of the water fractions. The increase in T1 and T2 relaxation times results in a high relative signal of multiple sclerosis lesions compared with adjacent normal brain on T2-weighted (long TR, long TE) images, irrespective of the stage of a lesion, and no difference or decreased signal intensity on T1-weighted (short TR, short TE) images. T1-weighted, contrast-enhanced MR imaging using intravenously administered moderate-molecular-weight gadolinium chelates (around 550 to 750 daltons) is also used to detect breaches in the normally intact blood-brain barrier that

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ABBREVIATIONS USED IN TEXT

EDSS = Expanded Disability Status Scale
IFN-β = interferon beta
IFNB = Interferon Beta-1b [trial]
MR = magnetic resonance
MSCRG = Multiple Sclerosis Collaborative Research Group [study]
MTI = magnetization transfer imaging

accompany the acute inflammatory stages of most multiple sclerosis lesions.

A multiple sclerosis lesion can be categorized as acute and new, acute and recurrent (both types typically gadolinium chelate-enhancing), and chronic (nonenhancing). The natural history of contrast-enhancing lesions and lesions that appear hyperintense on T2-weighted images (T2-hyperintense lesion) is depicted in Figures 1 and 2.

Acute-New Lesions

Acute-new lesions, defined as occurring de novo in normal and normal-appearing white matter, are predominantly inflammatory lesions, with perivascular cuffing, edema, and a mononuclear infiltrate.[10,11] These lesions range from 1 to 2 mm to several centimeters in diameter on T1- or T2-weighted images. Acute lesions in relapsing-remitting, secondary progressive, and benign disease have a disturbed blood-brain barrier, which is often the first sign of disease activity,[12-14] as indicated by regional gadolinium chelate enhancement (Figure 3-A and -B). In primary progressive disease, for reasons that are not yet understood, acute lesions are less likely to enhance,[15] but these, too, appear to be inflammatory, although to a lesser degree.[16] Superimposed on the regional contrast enhancement of acute lesions is a more extensive abnormality characterized by relative hyperintensity on T2-weighted

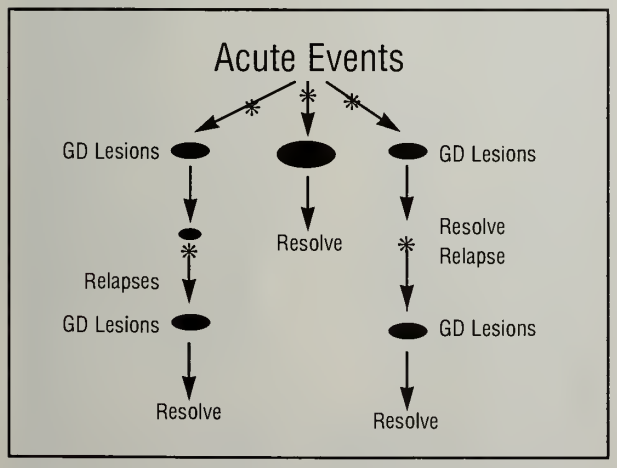

Figure 1.—Gadolinium-enhancing (**GD**) lesions are apparent because of a regional disruption of the normally intact blood-brain barrier (indicated by asterisks) and correspond to regions of focal inflammation seen on histopathologic examination. Such GD lesions typically remain visible by magnetic resonance imaging for a period of 2 to 8 weeks after onset and most often resolve completely. After they resolve, local recurrences (**Relapse**) may initiate another transient cycle until resolution.

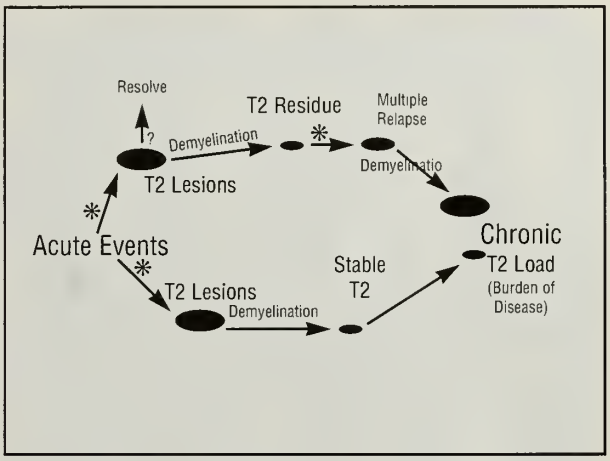

Figure 2.—Acute T2-hyperintense (**T2**) lesions, which are observed to overlap gadolinium-enhancing lesions, peak in area shortly after onset and then typically retract over a period of weeks, leaving a small scar, the T2 residue. T2 lesions may recur locally, a factor that may result in increased local tissue damage. The accumulated T2 residue(s) and acute T2 lesions result in what is observed as a T2-lesion load, or burden of disease. * = inflammatory response (influx of lymphocytes and macrophages and the production of cytokines and other mediators and immunoglobulin)

images, the high signal thought to be due primarily to local edema within and around an inflammatory lesion. Recent longitudinal short-echo–proton MR spectroscopy studies reveal lipids during the early stages (10 days) of the development of acute lesions that presumably are products of myelin breakdown.[17-19] The implication is that demyelination may occur relatively early, along with inflammation.[17] Other unspecified molecular markers can also be detected by in vivo MR spectroscopy in enhancing multiple sclerosis lesions.[20]

Over a period of two to eight weeks, the areas of contrast enhancement and T2 hyperintensity both retract (Figure 3-A to -D and Figure 4), the former almost always completely, the latter most frequently leaving a smaller lesion, the T2 residue.[21-22] The opportunity has not occurred for the histopathologic correlation of the T2 residue resulting from a single MR event; it is assumed, however, that this lesion would share most of the characteristics of a chronic multiple sclerosis lesion (discussed later), although possibly to a milder degree.

Recurrent Lesions

High-frequency serial MR studies suggest that after the initial acute event and lesion contraction, about a third or more lesions may undergo repeated relapses, either along their periphery or internally,[14,23-25] resulting in a new cycle of expansion and contraction. These changes may correspond to the superimposed new, demyelinating lesions in remyelinating (shadow) plaques described from autopsy material.[26] Both MR and histologic studies suggest heterogeneity in chronic multiple sclerosis lesions, presumably related to the degree and type of tissue destruction. Recurring activity within or adjacent to earlier lesions may be one mechanism of more severe damage,[26]

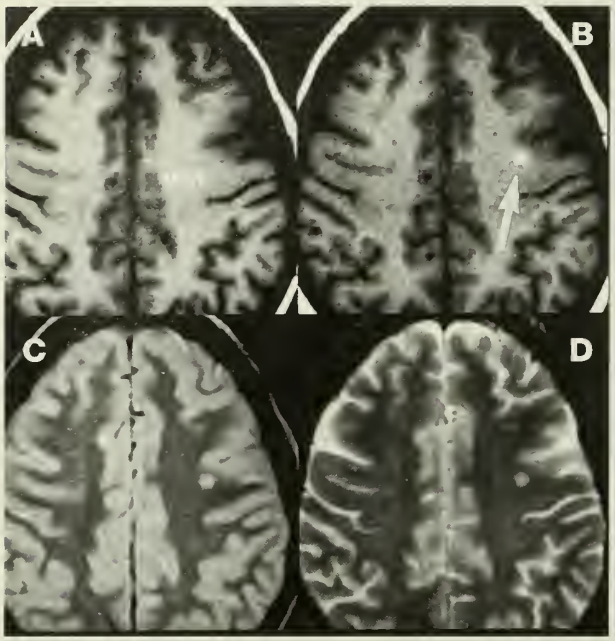

Figure 3.—The acute left frontal lesion is not well seen on the precontrast T1-weighted image (**A**), but becomes conspicuous on the contrast-enhanced image (**arrow in B**). The corresponding intermediate T2- and more T2-weighted images (**C** and **D**, respectively) show a T2-hyperintense lesion only slightly greater in area than the same lesion on the gadolinium-enhanced image (**B**).

although differential damage from single acute events—as a host response—or the initial severity of an isolated event may be alternative or additional mechanisms.

Chronic Lesions

Chronic multiple sclerosis lesions appear as focal or confluent regions of increased signal intensity on T2-weighted MR images. Most chronic lesions are accompanied by little or no visible change on anatomically corresponding T1-weighted images, whereas some chronic T2-hyperintense lesions appear to have corresponding T1-hypointense regions. The histopathologic features of chronic T2-hyperintense lesions almost certainly range widely from minimal demyelination (increased water space) to severe destructive demyelination with axonal loss. It has been proposed that T1-hypointense areas could represent regions of more severe tissue damage.[27,28] Autopsy-MR correlation shows most chronic lesions to be zones of myelin loss, with a relative preservation of axons, reactive astrogliosis, and little or no evidence of activity, as judged by the absence of inflammatory cells.[10,29,30]

In patients with large volumes of lesion, most of the T2-hyperintense lesion volume appears stable over years,[9] although month-to-month fluctuations in total lesion area are observed, and the natural history is one of gradual accumulation.[8,21,22,31] The accumulated lesion has become known as the lesion load or burden of disease.[32]

Magnetic Resonance Imaging Measures as Clinical Surrogates

Although multiple sclerosis lesions in the brain have a characteristic distribution, shape, and contrast-enhancement pattern that are helpful in the differential diagnosis,[9,33] these findings alone are not diagnostic of the disorder. False-positive diagnoses of multiple sclerosis

Figure 4.—T2-weighted images of the lesions shown in Figure 3 taken 1 (**left**) and 2 years (**right**) later show that the T2 residue (**arrows**) is about 50% of the initial lesion area. The lesion was nonenhancing at 1- and 2-year follow-ups (not shown).

based on MR imaging alone are far too common, and important disorders including neoplasms may mimic multiple sclerosis.[34]

This review focuses on MR-detected lesions in patients with a known or high probability of having multiple sclerosis (such as after a monosymptomatic attack suggestive of the disease), where these lesions take on a different meaning and importance. Based on observations of multiple sclerosis lesions in the brain, several MR measures have been described that are increasingly used as clinical surrogates. The relationship of these MR measures to clinical measures of disease are summarized in Table 1.

Sensitivity of Magnetic Resonance Imaging to Acute Disease

Most multiple sclerosis activity in the central nervous system is clinically silent, particularly in the brain, because lesions occur predominantly in the white matter. Although several autopsy series showed that the disease may go unnoticed during life,[35,36] the degree to which subclinical disease was missed was only fully appreciated after the development of MR imaging,[13,21,37,38] particularly with the introduction of frequent (monthly to every 6 weeks) serial MR studies.[22,39,40] Clinical relapses are reported to occur with a frequency of 0.1 to 1.2 events per year in most studies,[41] and rarely as many as 2 per year. Frequent serial MR studies, however, show that acute events (≥1 new lesions) are detected four to ten times more commonly than would be apparent by clinical observation alone.[22,40,42,43] In the Multiple Sclerosis Collaborative Research Group (MSCRG) study of relapsing multiple sclerosis, where clinical inactivity for at least two months was required for entry, 53% of 276 patients had active, gadolinium-enhancing lesions on their baseline MR examination.[44] The clinical-MR imaging discrepancies found in these studies is the result of only a small fraction of active lesions occurring, presumably by chance, in the more clinically sensitive locations, such as the optic nerve, brain stem, or spinal cord.

Magnetic Resonance Imaging as a Surrogate Measure of Clinical Disability

Clinical relapse rates do not correlate strongly, and are not predictive in a simple way, with subsequent clinical disability and prognosis.[41] Although the relapse frequency may decrease from the time of disease onset, disability tends to increase and assumes a more progressive course in most, although not all, patients.[41] For these reasons, and now the known insensitivity of the clinical relapse measure, many treatment trials have relegated the relapse rate to the level of a secondary measure of treatment outcome, in deference to measures of clinical disability, which are considered primary outcome measures.[44]

Clinical disability in patients with multiple sclerosis is unfortunately difficult to characterize in the absence of a satisfactory comprehensively analytic system. The most widely used measure is the Expanded Disability Status Scale (EDSS),[45] but the EDSS is well known to be weighted toward disturbances in locomotor function and to lack linearity, so that incremental steps are unequal. The EDSS is also relatively insensitive to cognitive and upper limb function.[7,46] This scale may also be too sensitive to acute events, which result in transient score elevations that do not accurately reflect persistent disability.

The MR surrogate to disability to date has been the accumulated T2-hyperintense lesion load (burden of disease). The best rationale for considering the lesion load as a surrogate measure of disability is that these lesions, which are predominantly stable, accumulate over time in both the brain and spinal cord and therefore reflect in a relatively direct manner patients' recent and remote pathologic history (surrogate in the first sense). Numerous studies indicate that the lesion load and disability do not correlate strongly. The correlation between disability

TABLE 1.—*Magnetic Resonance (MR) Imaging Compared With Clinical Measures of Disease*

Category	*Description*
Specificity	False-positive diagnosis of multiple sclerosis (MS) by MR imaging not uncommon; false-positive rate decreased but not eliminated using quantitative and strict qualitative MR imaging criteria
	False-negative diagnosis by MR imaging less common, but not zero
Sensitivity	After monosymptomatic attack,* positive brain MR imaging study moderately predictive of progression to clinical MS in 1-5 yr†
	After monosymptomatic attack, negative brain MR imaging study more strongly predictive against progression to clinical MS‡
Extent of disease	MR imaging frequently shows widely scattered lesions not detected by clinical examination
New lesion (attack) rate	Rate by MR imaging§ exceeds clinical rate by a factor of 4-10:1
Effects of disease	T2-hyperintense lesion load by MR imaging correlates poorly with clinical disability measures (such as EDSS)
Course of disease	The tempo of disease depicted by MR imaging§ may not correlate with pattern described by clinical observation (such as stable, relapsing, or progressive)

EDSS = Expanded Disability Status Scale

*Some examples are optic neuritis or brain stem or spinal cord syndrome resembling MS.
†False-positive tests are caused by acute disseminated encephalomyelitis and, more rarely, neoplastic, vascular, or inflammatory diseases mimicking MS.
‡Cases of clinically definite MS with negative brain MR imaging have been reported after spinal cord syndromes, however.
§Based on frequent MR imaging studies, for example, every 4 to 6 weeks.

and the lesion load is modest at best, on the order of 0.15 to 0.5 in most studies.[8,28,47,48] For the more homogeneous group of patients with clinically isolated syndromes suggestive of multiple sclerosis, however, the correlation between the T2-measured lesion load and the EDSS with a five-year follow-up is stronger.[49]

The imperfect correlation between disability and the MR-determined T2-hyperintense lesion load is at least in part the result of the nonspecific nature of T2-hyperintense lesions—that is, minimally damaged tissue (increased water space) is not differentiated from highly destructive changes (axonal loss and demyelination). Despite these limitations, MR-based measures of accumulated injury are appealing surrogate markers, as they are possibly more reproducible, quantitative measures than disability scores. For example, although the EDSS changed little in the IFNB trial from baseline in the placebo group,[3,8] MR progression (>10% increase in the T2-hyperintense lesion area) was documented in more than half of the subjects receiving placebo.[8] The low disability progression rates in patients that were observed in an optic neuritis treatment trial indicate that a large study population would be required to document treatment effects using disability progression alone (R. Beck, MD, PhD, Jaeb Center for Health Research, Tampa, Florida, oral communication, October 1995). Yet, investigators were able to show a progression of the lesion load after five years' follow-up in patients with monophasic presentations, where a median increment of 4.08 ml was observed in the subset of patients in whom multiple sclerosis developed during follow-up, from a baseline median of 1.15 ml.[49]

The equation relating the effect of a lesion of varying destructiveness placed in diverse anatomic and functional pathways and its clinical expression is no doubt complex. If the goal is to document pathologic events over time, the MR surrogates remain promising measures for monitoring treatment outcome. In addition, new outcome measures, discussed later, that are thought to be more specific measures of tissue damage than the T2-hyperintense lesion load, such as the magnetization transfer index (MTI), decreased *N*-acetyl aspartate levels, and the T1-hypointense lesion load, may improve the MR imaging-disability correlations.

Characterization of Disease Course by Magnetic Resonance Compared With Clinical Criteria

Multiple sclerosis manifests in several ways—including as relapsing-remitting disease, which evolves in most cases to a progressive course, and, more rarely, as benign or primary progressive forms. The classification of cases into these categories of disease is based on clinical observations—predominantly the relapse rate, disability, and disability progression. Although treatment trials commonly use patient selection criteria based on these categorizations, clinical disease patterns vary over short intervals.[50] Magnetic resonance activity has been recently used as an entrance requirement in several high-frequency serial MR studies of multiple sclerosis, and there is interest in using MR-based criteria as disease classification variables in future treatment trials.

Monosymptomatic patients, who technically do not meet criteria for clinical multiple sclerosis, are a particularly interesting clinical subgroup because they provide an opportunity to observe multiple sclerosis at its earlier stages. Conversion to clinical disease in one to five years occurs in from 23% to 93% of monosymptomatic patients who on initial MR examination have multifocal, asymptomatic brain lesions indistinguishable from multiple sclerosis. This is in contrast to a 4% conversion rate in patients with negative MR examinations of the brain.[51] A requirement for typical multiple sclerosis lesions on an MR screening study on monosymptomatic presentation provides an efficient mechanism for eliminating as many as two thirds of the patients who are unlikely to benefit from long-term therapy and improves the likelihood of detecting a treatment effect such as delaying or decreasing the development of clinical multiple sclerosis or its surrogate measures.

The use of MR criteria in other patient groups is less straightforward. Patients with primary and secondary progressive multiple sclerosis have different MR imaging patterns,[52,53] with greater gadolinium contrast enhancement occurring in patients with secondary progressive (67%) compared with primary progressive (14%) disease. There may be no fundamental differences in MR activity, however, between relapsing and progressive multiple sclerosis. It has in fact been suggested that the clinical phenotype may be less important than whether there is ongoing clinical or MR imaging evidence of disease activity.[53]

Results from the MSCRG study underscore the possible use of MR-based measures rather than clinical criteria alone. Despite a restricted range of clinical entrance criteria including disability (1 to 3.5), age, disease course (relapsing-remitting), and relapse rate (0.67 exacerbations per year during the previous 3 years), the MSCRG showed a large variation in brain lesion volume on entrance, ranging from 0 to 62 ml (the latter large and confluent), and a wide range in the number of gadolinium-enhancing lesions, from 0 to 56.[44]

Magnetic Resonance-Based Measures of Treatment Response

Several MR-based measures will be used in new multiple sclerosis clinical trials. The background and details of these study designs are summarized in several recent reports.[7,39,51,54] The basic strategies include phase I and II trials of relapsing-remitting and secondary-progressive disease designed around serial, monthly MR imaging, with the treatment effect determined by a decrease in the number of gadolinium-enhancing or new or enlarging or recurrent T2 lesions. Based on the results of the phase I and II studies, promising therapeutic interventions will be tested by more definitive phase III clinical trials. The monthly MR strategy allows analyses of preliminary treatment efficacy in periods of only 6 to 12 months, rather than the two to three years required for meaningful

clinical outcome-based studies.[39,54] Phase III trials are designed around clinical outcome measures, but will typically include secondary MR-based outcomes using monthly MR studies in subgroups, the annual change in the T2-hyperintense lesion load, and new or enlarging lesion analyses in the full study population.[51]

Magnetic resonance-based measures for treatment trials include the following variables:

- Acute activity—rate of development of gadolinium-enhancing lesions and new, enlarging, and recurrent T2-hyperintense lesions that in monthly studies are surrogates to measures of the clinical relapse rate;
- Accumulating burden of disease, including the T2-lesion volume, and the total number of new or enlarging T2 lesions over one to several years;
- Specific measures of the accumulating burden of disease—the volume of T1-hypointense lesions, MTI indices, a decrease in the *N*-acetyl aspartate level—that are potentially stronger surrogates for disability. Other measures of accumulated disease include global atrophy measures—corpus callosum and spinal cord area.

Acute Lesion Rates

Acute lesions are easily and reliably detected using gadolinium chelate-enhanced T1-weighted imaging, or alternatively by new T2-hyperintense lesion counts. Determining the number of gadolinium-enhanced lesions is more sensitive than counting the T2-hyperintense lesions,[55] although the latter may be helpful when the interval between MR studies is long. A median of 3 (mean, 4.9) active lesions (new plus enlarging plus recurrent) per year was observed in the placebo arm of the 52-patient relapsing-remitting cohort in the IFNB study, based on MR studies obtained at six-week intervals for two years.[8] In a group of 14 patients with active relapsing-remitting disease, a mean of 2.73 new gadolinium-enhanced lesions per month was observed.[56] In an earlier study, a mean of 2.3 gadolinium-enhanced lesions per month was reported in seven patients with relapsing-remitting disease.[40]

The interpatient variation in gadolinium-enhanced lesion activity exceeds the intrapatient variation,[54] although the latter can be considerable. Despite the now known pronounced variation in gadolinium-enhanced lesion number and volume over short intervals in patients selected for active disease, annual counts of gadolinium-enhanced lesions were nevertheless effective treatment measures in the phase III IFN B-1a trial,[44,57] revealing a significant treatment effect in the reduction of new multiple sclerosis lesions in the brain.[57,58]

T2-Hyperintense Lesion Volume

The T2-hyperintense lesion volume is a composite measure of the volume of chronic (mostly stable) disease and acute lesions. Large month-to-month and year-to-year fluctuations in T2-lesion volumes have been observed.[8,31] Fluctuation may be the result of a changing mix of acute and chronic lesions, volume quantitation errors induced by a change in scan-to-scan MR acquisition factors (such as scan angle and slice position), and measurement error, which was described in the initial study results from the IFNB and MSCRG trials.[8,57-59]

The intrapatient percentage of T2-lesion area or volume change during a treatment trial is expected to vary according to the baseline T2 volume and the disease activity of the population being studied, but based on the natural history of the disease and given sufficient follow-up, it should increase in a large population study. For example, a median T2-lesion area increase of 15% over three years was observed in the placebo arm of the IFNB trial.[8] It is expected that an improved acquisition technique, for example, MR acquisitions with 3-mm slice thicknesses, and more statistical-based computerized approaches to quantitating white matter lesions should substantially improve the effectiveness of the T2 measure in future trials.[59-61]

Magnetization Transfer Imaging

Magnetization transfer imaging is thought to be sensitive to myelin destruction because it measures the exchange of magnetization between bound water fractions, in the vicinity of MR-invisible macromolecules (such as myelin), with free (visible) water fractions. Although direct MR-histopathologic evidence is limited in humans and in studies of animals, there have been repeated suggestions that MTI distinguishes, more so than conventional T2-weighted MR imaging, demyelination from less important disease such as edema.[62,63] The gain in specificity of MTIs over the T2-lesion load may account for the improved correlation of MTIs and disability compared with the T2-lesion load and disability.[48]

T1 Hypointensity

Although the heterogeneity of lesions on T1-weighted images has long been recognized, T1 hypointensity has only recently come under scrutiny as a possible marker for greater tissue destruction in multiple sclerosis, comparable to decreased MTIs.[28,64] T1 hypointensity and MTI-based measures are both feasible using commercial MR imaging systems.

Proton MR Spectroscopy

Multiple sclerosis lesions frequently have a lower-than-normal *N*-acetyl aspartate concentration, presumed to indicate decreased neuronal or axonal density or an abnormally low concentration of *N*-acetyl aspartate in the sampled axons.[18,65,66] Transient decreases in *N*-acetyl aspartate in acute lesions, followed by recovery, suggest that it may not simply measure axonal loss alone,[17] as cellular recovery to the observed degree is not to be expected.

Measuring Atrophy

Corpus callosum atrophy observed at autopsy or in vivo probably reflects a combination of local damage and global cerebral injury.[67,68] A decreased corpus callosum size has been shown to correlate with specific areas of neuropsychological dysfunction in multiple sclerosis.[69,70]

It is not yet known if progressive corpus callosum atrophy can be reliably determined in one- to two-year treatment trials. Spinal cord atrophy is also of interest because spinal involvement is known to contribute strongly to clinical disability and poor disability indexes.[71]

Conclusion

Magnetic resonance imaging provides a direct, objective, quantitative measure of the extent, progression, and tempo of multiple sclerosis lesion activity in the brain. Effective entry into treatment trials and treatment outcome measures based on MR imaging are now feasible. Verification and improvements in these measures, including more specific tissue-destruction indexes, improved methods for analyzing spinal cord involvement, and improved statistical-based volumetric methods will be important contributions in the next few years. More specific and objective MR-based measures of disease in vivo are feasible. It should be possible to analyze the individual components of the demyelination cascade. For example, once there has been a breach of the blood-brain barrier (as indicated by gadolinium enhancement), treatment may differentially affect the outcome (size) of the acute lesion as indicated by the area of T2-hyperintense lesions, compared with the size of the final long-term T2 residue. In conjunction with new and more specific immunomodulatory and combined therapies, it can be anticipated that MR measures will continue to play an important role in the development of effective multiple sclerosis therapies.

REFERENCES

1. Kurtzke JF: Epidemiology of multiple sclerosis, *In* Vinken PJ, Bruyn GW, Klawans HL (Eds): Handbook of Clinical Neurology, Vol 3—Demyelinating Diseases. Amsterdam, The Netherlands, Elsevier Science Publishers, 1985, pp 259-287

2. Matthews WB: Clinical aspects, *In* Matthews WB (Ed): McAlpine's Multiple Sclerosis. New York, NY, Churchill Livingstone, 1991, pp 43-79

3. IFNB Multiple Sclerosis Study Group: Interferon beta-1b is effective in relapsing-remitting multiple sclerosis—I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43:655-661

4. Jacobs L, Johnson KP: A brief history of the use of interferons as treatment of multiple sclerosis. Arch Neurol 1994; 51:1245-1252

5. Weinstock-Guttman B, Ransohoff RM, Kinkel RP, Rudick RA: The interferons: Biological effects, mechanisms of action, and use in multiple sclerosis. Ann Neurol 1995; 37:7-14

6. Goodkin DE: Role of steroids and immunosuppression and effects of interferon beta-1b in multiple sclerosis. West J Med 1994; 161:292-298

7. Whitaker JN, McFarland HF, Rudge P, Reingold SC: Outcomes assessment in multiple sclerosis clinical trials: A critical analysis. Multiple Sclerosis 1995; 1:37-47

8. Paty DW, Li DKB, UBC MS/MRI Study Group, IFNB Multiple Sclerosis Study Group: Interferon beta-1b is effective in relapsing-remitting multiple sclerosis—II. MRI analysis results of a multicenter, randomized, double blind, placebo controlled trial. Neurology 1993; 43:662-667

9. Simon JH: Neuroimaging of multiple sclerosis. Neuroimaging Clin North Am 1993; 3:229-246

10. Katz D, Taubenberger JK, Cannella B, McFarlin DE, Raine CS, McFarland HF: Correlation between magnetic resonance imaging findings and lesion development in chronic, active multiple sclerosis. Ann Neurol 1993; 34:661-669

11. Nesbit GM, Forbes GS, Scheithauer BW, Okazaki H, Rodriguez M: Multiple sclerosis: Histopathologic and MR and/or CT correlation in 37 cases at biopsy and three cases at autopsy. Radiology 1991; 180:467-474

12. Kermode AG, Thompson AJ, Tofts P, et al: Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis—Pathogenetic and clinical implications. Brain 1990; 113(pt 5):1477-1489

13. Kermode AG, Tofts PS, Thompson AJ, et al: Heterogeneity of blood-brain barrier changes in multiple sclerosis: An MRI study with gadolinium-DTPA enhancement. Neurology 1990; 40:229-235

14. Miller DH, Rudge P, Johnson G, et al: Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. Brain 1988; 111:927-939

15. Thompson AJ, Kermode AG, Wicks D, et al: Major differences in the dynamics of primary and secondary progressive multiple sclerosis. Ann Neurol 1991; 29:53-62

16. Revesz T, Kidd D, Thompson AJ, Barnard RO, McDonald WI: A comparison of the pathology of primary and secondary progressive multiple sclerosis. Brain 1994; 117:759-765

17. Davie CA, Hawkins CP, Barker GJ, et al: Serial proton magnetic resonance spectroscopy in acute multiple sclerosis lesions. Brain 1994; 117(pt 1):49-58

18. Richards TL: Proton MR spectroscopy in multiple sclerosis: Value in establishing diagnosis, monitoring progression, and evaluating therapy. AJR Am J Roentgenol 1991; 157:1073-1078

19. Narayana PA, Wolinsky JS, Jackson EF, McCarthy M: Proton MR spectroscopy of gadolinium-enhanced multiple sclerosis plaques. J Magn Reson Imaging 1992; 2:263-270

20. Grossman RI, Lenkinski RE, Ramer KN, et al: MR proton spectroscopy in multiple sclerosis. AJNR Am J Neuroradiol 1992; 13:1535-1543

21. Isaac C, Li DK, Genton M, et al: Multiple sclerosis: A serial study using MRI in relapsing patients. Neurology 1988; 38:1511-1515

22. Willoughby EW, Grochowski E, Li DK, Oger J, Kastrukoff LF, Paty DW: Serial magnetic resonance scanning in multiple sclerosis: A second prospective study in relapsing patients. Ann Neurol 1989; 25:43-49

23. Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF: Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: Implications for clinical trials and natural history. Ann Neurol 1991; 29:548-555

24. Koopmans RA, Li DK, Oger JJ, et al: Chronic progressive multiple sclerosis: Serial magnetic resonance brain imaging over six months. Ann Neurol 1989; 26:248-256

25. Smith ME, Stone LA, Albert PS, et al: Clinical worsening in multiple sclerosis is associated with increased frequency and area of gadopentetate dimeglumine-enhancing magnetic resonance imaging lesions. Ann Neurol 1993; 33:480-489

26. Prineas JW, Barnard RO, Revesz T, Kwon EE, Sharer L, Cho ES: Multiple sclerosis—Pathology of recurrent lesions. Brain 1993; 116(pt 3):681-693

27. Uhlenbrock D, Sehlen S: The value of T1-weighted images in differentiation between MS, white matter lesions, and subcortical arteriosclerotic encephalopathy (SAE). Neuroradiology 1989; 31:203-212

28. Van Walderveen MAA, Barkhof F, Hommes OR, et al: T1 SE More Specific Than T2 SE in Identifying Disabling Lesions in Multiple Sclerosis—A Quantitative Follow-up Study (Abstr). Proceedings of the Society of Magnetic Resonance Medicine, San Francisco, California, 1994, A536

29. Barnes D, Munro PM, Youl BD, Prineas JW, McDonald WI: The longstanding MS lesion—A quantitative MRI and electron microscopic study. Brain 1991; 114(pt 3):1271-1280

30. Newcombe J, Hawkins CP, Henderson CL, et al: Histopathology of multiple sclerosis lesions detected by magnetic resonance imaging in unfixed postmortem central nervous system tissue. Brain 1991; 114:1013-1023

31. Stone LA, Albert PS, Smith ME, et al: Changes in the amount of diseased white matter over time in patients with relapsing-remitting multiple sclerosis. Neurology 1995; 45:1808-1814

32. Paty DW, Li DK, Oger JJ, et al: Magnetic resonance imaging in the evaluation of clinical trials in multiple sclerosis. Ann Neurol 1994; 36 Suppl:S95-S96

33. Jacobs L, Simon JH: Neuroimaging of multiple sclerosis and related disorders, chap 17, *In* Greenberg JO (Ed): Neuroimaging—A Companion to Adams and Victor's Principles of Neurology. New York, NY, McGraw-Hill, 1995, 479-502

34. Case 31-1995: Case records of the Massachusetts General Hospital. N Engl J Med 1995; 333:992-999

35. Gilbert JJ, Sadler M: Unsuspected multiple sclerosis. Arch Neurol 1983; 40:533-536

36. Phadke JG, Best PV: Atypical and clinically silent multiple sclerosis: A report of 12 cases discovered unexpectedly at necropsy. J Neurol Neurosurg Psychiatry 1983; 46:414-420

37. Grossman RI, Braffman BH, Brorson JR, Goldberg HI, Silberberg DH, Gonzalez-Scarano F: Multiple sclerosis: Serial study of gadolinium-enhanced MR imaging. Radiology 1988; 169:117-122

38. Koopmans RA, Li DK, Oger JJ, Mayo J, Paty DW: The lesion of multiple sclerosis: Imaging of acute and chronic stages. Neurology 1989; 39:959-963

39. McFarland HF, Frank JA, Albert PS, et al: Using gadolinium-enhanced magnetic resonance imaging lesions to monitor disease activity in multiple sclerosis. Ann Neurol 1992; 32:758-766

40. Barkhof F, Scheltens P, Frequin STFM, et al: Relapsing-remitting multiple sclerosis—Sequential enhanced MR imaging vs clinical findings in determining disease activity. AJR Am J Roentgenol 1992; 159:1041-1047

41. Weinshenker BG, Ebers GC: The natural history of multiple sclerosis. Can J Neurol Sci 1987; 14:255-261

42. Thompson AJ, Miller D, Youl B, et al: Serial gadolinum-enhanced MRI in relapsing/remitting multiple sclerosis of varying disease duration. Neurology 1992; 42:60-63

43. Frank JA, Stone LA, Smith ME, Albert PS, Maloni H, McFarland HF: Serial contrast-enhanced magnetic resonance imaging in patients with early relapsing-remitting multiple sclerosis: Implications for treatment trials. Ann Neurol 1994; 36 Suppl:S86-S90

44. Jacobs L, Cookfair D, Rudick R, et al: A phase III trial of intramuscular recombinant interferon beta as treatment for exacerbating-remitting multiple sclerosis: Design and conduct of study and baseline characteristics of patients. Multiple Sclerosis 1995; 1:118-135

45. Kurtzke JF: Rating neurological impairment in multiple sclerosis: An Expanded Disability Status Scale (EDSS). Neurology 1993; 33:1444-1452

46. Noseworthy JH, Vandervoort MK, Wong CJ, Ebers GC: Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in multiple sclerosis clinical trials. Neurology 1990; 40:971-975

47. Filippi M, Paty DW, Kappos L, et al: Correlations between changes in disability and T2-weighted brain MRI activity in multiple sclerosis—A follow-up study. Neurology 1995; 45:255-260

48. Gass A, Barker GJ, Kidd D, et al: Correlation of magnetization transfer ratio with clinical disability in multiple sclerosis. Ann Neurol 1994; 36:62-67

49. Filippi M, Horsfield MA, Morrissey SP, et al: Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology 1994; 44:635-641

50. Goodkin DE, Hertsgaard D, Rudick RA: Exacerbation rates and adherence to disease type in a prospectively followed-up population with multiple sclerosis: Implications for clinical trials. Arch Neurol 1989; 46:1107-1112

51. Miller DH, Albert PS, Barkhof F, et al: Guidelines for the use of magnetic resonance techniques in monitoring the treatment of multiple sclerosis. Ann Neurol 1996; 39:6-16

52. Thompson AJ, Kermode AG, MacManus DG, et al: Patterns of disease activity in multiple sclerosis: Clinical and magnetic resonance imaging study. BMJ 1990; 300:631-634

53. Wiebe S, Lee DH, Karlik SJ, et al: Serial cranial and spinal cord magnetic resonance imaging in multiple sclerosis. Ann Neurol 1992; 32:643-650

54. Nauta JJP, Thompson AJ, Brakhof F, Miller DH: Magnetic resonance imaging in monitoring the treatment of multiple sclerosis patients: Statistical power of parallel-groups and crossover designs. J Neurol Sci 1994; 122:6-14

55. Miller DH, Barkhof F, Nauta JJP: Gadolinium enhancement increases the sensitivity of MRI in detecting disease activity in multiple sclerosis. Brain 1993; 116:1077-1094

56. Stone LA, Frank JA, Albert PS, et al: The effect of interferon-beta on blood-brain-barrier disruptions demonstrated by contrast-enhanced magnetic resonance imaging in relapsing-remitting multiple sclerosis. Ann Neurol 1995; 37:611-619

57. Jacobs L, Cookfair D, Rudick R, et al: Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996; 39:285-294

58. Simon JH, Jacobs L, Cookfair D, et al: The natural history of MS based on an annual MR snapshot: Results from the MSCRG study of intramuscular recombinant interferon beta-1a (Abstr). Neurology 1995; 45(suppl 4):A418

59. Simon JH, Li X, Scherzinger A: Quantitative Determination of T2-Lesion Volume in Multiple Sclerosis: The Error of Serial Studies (Abstr). Proceedings of the American Society of Neuroradiology, Chicago, Illinois, 1995, A204

60. Kikinis R, Shenton ME, Gerig G, et al: Routine quantitative analysis of brain and cerebrospinal fluid spaces with MR imaging. J Magn Reson Imaging 1992; 2:619-629

61. Mitchell JR, Karlik SJ, Lee DH, Fenster A: Computer-assisted identification and quantification of multiple sclerosis lesions in MR imaging volumes in the brain. J Magn Reson Imaging 1994; 4:197-208

62. Dousset V, Grossman RI, Ramer KN, et al: Experimental allergic encephalomyelitis and multiple sclerosis: Lesion characterization with magnetization transfer imaging. Radiology 1992; 182:483-491 [erratum published in Radiology 1992; 183:878]

63. Dousset V, Brochet B, Vital A, et al: Lysolecithin-induced demyelination in primates: Preliminary in vivo study with MR and magnetization transfer. AJNR Am J Neuroradiol 1995; 16:225-231

64. Hiehle JF, Grossman RI, Ramer KN, et al: Magnetization transfer effects in MR-detected multiple sclerosis: Comparison with gadolinium-enhanced spin-echo images and non-enhanced T1-weighted images. AJNR Am J Neuroradiol 1995; 16:69-77

65. Arnold DL, Riess GT, Matthews PM, et al: Use of proton magnetic resonance spectroscopy for monitoring disease progression in multiple sclerosis. Ann Neurol 1994; 36:76-82

66. Larsson HBW, Christiansen P, Jensen M, et al: Localized in vivo proton spectroscopy in the brain of patients with multiple sclerosis. Magn Reson Med 1991; 22:23-31

67. Barnard RO, Triggs M: Corpus callosum in multiple sclerosis. J Neurol Neurosurg Psychiatry 1974; 37:1259-1264

68. Simon JH, Schiffer RB, Rudick R, Herndon RM: Quantitative determination of MS-induced corpus callosum atrophy in vivo using MR imaging. AJNR Am J Neuroradiol 1987; 8:599-604

69. Rao SM, Leo GJ, Haughton VM, St Aubin-Faubert P, Bernardin L: Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. Neurology 1989; 39(pt 1):161-166

70. Pelletier J, Habib M, Lyon-Caen O, Salamon G, Poncet M, Khalil R: Functional and magnetic resonance imaging correlates of callosal involvement in multiple sclerosis. Arch Neurol 1993; 50:1077-1082

71. Kidd D, Thorpe JW, Thompson AJ, et al: Spinal cord MRI using multi-array coils and fast spin echo—II. Findings in multiple sclerosis. Neurology 1993; 43:2632-2637

Conferences and Reviews

Differential Diagnoses of Bone Marrow Granuloma

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The finding of a granuloma on a bone marrow biopsy is not common. The etiologic spectrum encompasses a wide variety of disorders. We present the case of a young woman with a bone marrow granuloma and discuss the differential diagnosis, emphasizing the most common causes. This disorder can be associated with serious diseases.

(Eid A, Carion W, Nystrom JS: Differential diagnoses of bone marrow granuloma. West J Med 1996; 164:510-515)

Bone marrow granuloma is not a frequent finding in a bone marrow biopsy. The incidence ranges from 0.3% to 2.2%, depending on the series.[1-5] A large number of cases was first published in 1950.[3] Many diseases have been implicated in the formation of granulomas in the bone marrow, but they are not specific and do not usually show characteristic features that typify a specific diagnosis. We report the case of a young woman with fever, anemia, and a bone marrow granuloma. We review the differential diagnosis and the literature, including five major studies of bone marrow granuloma.

Report of a Case

The patient, a 19-year-old woman, was seen because of fever and shortness of breath on exertion. These symptoms had been present for a week before admission. She had no other symptoms. Her history was relevant only for a cholecystectomy at age 16. She said she did not use tobacco, alcohol, or drugs of abuse and was taking acetaminophen for her fever.

On physical examination, the patient was obese but in no distress. Her blood pressure was 130/75 mm of mercury, pulse rate 100 beats per minute, and temperature 39.5°C (103°F). She had no palpable cervical lymph nodes, and no other abnormalities were noted.

Laboratory test results are shown in Table 1. Her chest x-ray film was unremarkable: no infiltrate, effusions, hilar abnormalities, or other findings were noted. A computed tomographic (CT) scan of the chest showed no abnormalities. A CT scan of the abdomen showed mild splenomegaly and multiple enlarged lymph nodes in the periaortic area. A skin test for *Candida* species, mumps, and purified-protein derivative showed anergy.

During the initial evaluation, a lymphoma was strongly suspected. A bone marrow biopsy specimen showed only a noncaseating granuloma without any signs of lymphoma (Figures 1 and 2). Despite stains for acid-fast bacilli (AFB), fungus, Gram's stains, immunophenotyping, and several histologic studies, no definitive diagnosis could be established. Tests for antibodies to the human immunodeficiency virus (HIV) were negative, as were those for cytomegalovirus, *Histoplasma capsulatum*, and *Brucella* species. A sputum specimen did not show any mycobacteria.

The patient underwent exploratory laparotomy with diagnostic splenectomy and multiple biopsies. All showed noncaseating granulomas. An angiotensin-converting enzyme (ACE) level was elevated. Empirical therapy for tuberculosis with isoniazid and rifampin was initiated while culture results were pending. There was no improvement with this treatment after two weeks. No bone marrow, liver, lymph node, or spleen specimen grew any pathogen after eight weeks. The final diagnosis of sarcoidosis was made. A trial of steroid therapy was successful, and the patient was doing well two months after discharge from the hospital.

Discussion

Many disorders have been implicated in the pathogenesis of bone marrow granuloma. They encompass many unrelated diseases including malignant lesions; viral, bacterial, and fungal infections; autoimmune diseases; drugs; and sarcoidosis. Although some specific pathologic findings can point toward certain diagnoses—for instance, caseation in tuberculosis, Reed-Sternberg cells in Hodgkin's lymphoma, poorly organized granulomas in HIV infection—these findings are uncommonly seen in the marrow. Frequently the diagnosis cannot be made solely on pathologic criteria. Rather, it will have to be based on epidemiologic, clinical, laboratory, and radiologic data.

Tables 2 and 3 list the most frequent causes of bone marrow granuloma in five studies.[1-5]

Malignant neoplasms have been reported as the cause of bone marrow granulomas in 20% to 25% of the cases,

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CT = computed tomographic
EBV = Epstein-Barr virus
HIV = human immunodeficiency virus

most being malignant lymphomas of the Hodgkin's and non-Hodgkin's type, the Hodgkin's type being more frequent.[1-5] A bone marrow granuloma occurring in patients with Hodgkin's disease is uncommon.[6-8] An incidence of bone marrow granuloma of 5% has been reported in patients with known Hodgkin's lymphoma.[8] The finding of a Reed-Sternberg cell within the granuloma is rare.[2,3,6]

A bone marrow granuloma in patients with lymphoma can be due to the invasion of the bone marrow or, more frequently, a nonspecific immunologic change due to cancer. Its presence has been associated with a good prognosis in patients with Hodgkin's disease.[6,9]

Granulomas associated with a good prognosis have been described to be composed of groups of epithelioid histiocytes with occasional giant cells and no Reed-Sternberg cells. They are commonly distributed in a paravascular location. They cannot be considered evidence of invasion of the bone marrow.[6] A distinction should be made between epithelioid granulomas and lipogranulomas, frequently seen after lymphangiography in patients with Hodgkin's disease and carrying no prognostic importance.[10]

Distinguishing between sarcoidosis and Hodgkin's disease granuloma can be difficult if based on pathologic criteria only. Some authors are reporting an increased incidence of Hodgkin's disease in patients with sarcoidosis. The coexistence of both is possible. The following criteria are suggested for the diagnosis of duality: a biopsy obtained from an unrelated site, with clinical, radiologic, and biologic correlation.[11]

In general, it is rare for a non-Hodgkin's lymphoma to present initially as a bone marrow granuloma. In one study, 10 of 372 patients with known non-Hodgkin's lymphoma (2.7%) had bone marrow granulomas.[12] In non-Hodgkin's lymphoma, especially with follicular small cleaved cells, mixed small cleaved cells, and large cells, granulomatous lesions are sometimes observed. Such lesions consist of a large cell center surrounded by small cells and clusters of epithelialized histiocytes, giving the appearance of a granuloma. Distinguishing this lesion from a true epithelioid granuloma can be difficult. Immunophenotyping can be helpful in such cases.[13]

Many other malignant neoplasms have been associated with bone marrow granulomas.[1-3,9,14,15] The diagnosis is usually easily made in these cases, as the cancer is usually in an advanced stage.

Infectious causes occupy a major place in the differential diagnosis of bone marrow granulomas. Bacterial, viral, fungal, and parasitic infections have been reported. Brucellosis is a frequent and well-established cause. The incidence of brucellosis ranged between 0% and 12.5%,[1-4] and bone marrow granulomas were found in 28% to 68% of cases.[16,17] Granulomas consist of epithelialized cells surrounded by lymphocytes, plasmocytes, and occasional Langhans' cells.[3] Cytophagocytosis was commonly seen, but caseating necrosis is absent.[16] Serologic tests and bone marrow cultures are usually positive (86% and 92%, respectively).[18]

Typhoid fever is another common cause of bone marrow granuloma. In a study in Spain, the incidence of typhoid fever was 10%.[4] Chronic granulomatous inflammation was the most common finding on bone marrow biopsies and was associated with hemophagocytosis.[19] Bone marrow cultures were more sensitive than blood cultures for organism recovery.[20]

Many authors have reported Q fever to be a classic cause of bone marrow granulomas.[21] In a report of seven bone marrow biopsies in patients with Q fever, all seven had a granuloma.[22] Five showed nonspecific findings,

TABLE 1.—*Laboratory Test Results on a Young Woman With Unexplained Fever*

Test	*Result, SI Units*	*(Conventional)*
Hemoglobin, grams/liter (grams/dl)	80	(8.0)
Hematocrit, fraction of 1 (%)	0.24	(24)
MCV, fl (μm^3)	85	(85)
Leukocyte count, $\times 10^9$/liter (cells/mm^3)	6	(6,000)
Platelet count, $\times 10^9$/liter (/mm^3)	450	(450,000)
Electrolytes	Normal	
BUN and creatinine	Normal	
Iron, μmol/liter (μg/dl)*	6	(32)
Total iron-binding capacity, μmol per liter (μg/dl)†	43	(241)
Ferritin, μg/liter (ng/ml)‡	150	(150)
Reticulocyte count, fraction of 1 (%)	0.01	(1)
Haptoglobin, grams/liter (mg/dl)§	1.48	(148)
Vitamin B_{12}, pmol/liter (pg/ml)‖	830	(1,130)
Erythrocyte folate, nmol/liter (ng/ml)¶	1,790	(790)
ESR, mm/hour	>100 mm/sec	
Alkaline phosphatase, U/liter#	500	
AST (SGPT), U/liter**	50	
ALT (SGOT), U/liter††	40	
ACE level, nmol·$liter^{-1}$·sec^{-1}(nmol/ml/min)‡‡	1,630	(98)
Antinuclear and anti-DNA antibody tests	Negative	
Rheumatoid factor	Negative	
Coombs' direct and indirect	Negative	
Ham test	Negative	

ACE = angiotensin-converting enzyme, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, MCV = mean corpuscular volume, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase, SI = Système International

*Normal, 7 to 27 μmol/liter (40 to 150 μg/dl).
†Normal, 39 to 72 μmol/liter (220 to 400 μg/dl).
‡Normal, 10 to 107 μg/liter (10 to 107 ng/ml).
§Normal, 0.13 to 1.63 grams/liter (13 to 163 mg/dl).
‖Normal, 162 to 693 pmol/liter (220 to 940 pg/ml).
¶Normal, 280 to 1,360 nmol/liter (125 to 600 ng/ml).
#Normal, 15 to 110 U/liter.
**Normal, 0 to 45 U/liter.
††Normal, <670 nmol·$liter^{-1}$·sec^{-1} (<40 nmol/ml/min).
‡‡Normal, 8 to 52 U/liter.

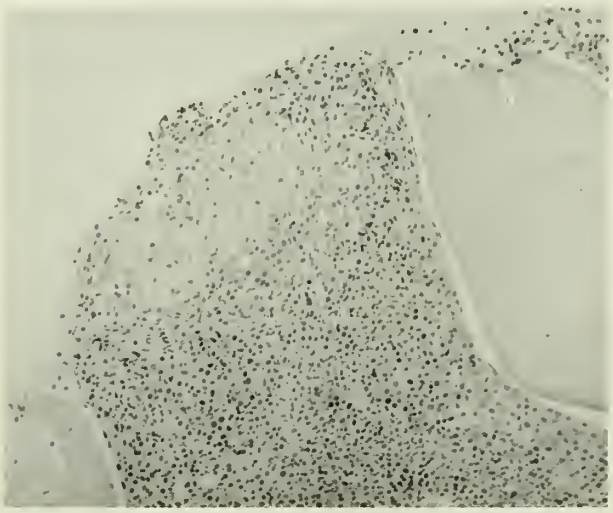

Figure 1.—A section of the bone marrow shows granuloma (hematoxylin and eosin stain, original magnification ×10).

and two had the classical finding for Q fever: the "donut" lesion (or fibrin-ring granuloma) that consists of a central empty space (probably an adipocyte), surrounded by lymphocytes and a characteristic fibrin ring. Serologic tests are usually positive.[21,22] Fibrin-ring granulomas, once thought to be characteristic of Q fever, can be seen in patients with Hodgkin's disease,[23,24] cytomegalovirus (CMV),[25] Epstein-Barr virus (EBV) infection,[26] hepatitis A,[27] giant cell arteritis,[23] leishmaniasis,[28] and allopurinol hepatitis.[24,29]

Tuberculosis is one of the most frequent causes of bone marrow granuloma; it constitutes 6% to 48% of the cases.[1-5] In cases of miliary tuberculosis, 33% to 100% of bone marrow biopsies will show granulomas. Yet, caseating necrosis is uncommon (29%), and the presence of AFB by the Ziehl-Neelsen stain is rare.[30] Marrow patchy necrosis can be seen. The lowest recovery of organisms by culture was from the bone marrow—15% compared with 78% from the sputum.[5] In patients with the acquired immunodeficiency syndrome (AIDS) with diagnosed disseminated tuberculosis and bone marrow granulomas, cultures of the bone marrow were positive in less than 50% of the cases.[31]

In a review of 13 patients with disseminated *Mycobacterium avium-intracellulare* who had a bone marrow biopsy, 9 (69) had a bone marrow granuloma.[32] No necrosis or caseation was found in any of the granulomas. Staining for AFB was positive in only one case. Cultures for *M avium-intracellulare* were positive in 7 of the patients.[32]

Bone marrow granulomas have been described in the marrow of patients with disseminated bacillus Calmette-Guérin infection following vaccination.[33,34] The granulomas were noted to be noncaseating in all four patients who had a bone marrow biopsy.[34]

Disseminated fungal infections rank high on the differential diagnosis of bone marrow granuloma. With the spread of HIV, it is expected that the incidence of these diseases will rise, with histoplasmosis being the leading cause. The incidence of histoplasmosis varied among the different studies. In contrast to a Spanish study in which an incidence of 0% was found,[4] the study by Boden showed an incidence of 20%.[2] This finding might be due to epidemiologic factors. In immunocompromised patients, the chances of dissemination to the bone marrow are high. In a study of 58 immunocompromised patients infected with histoplasmosis, 33 had histoplasmosis in the bone marrow.[35] Bone marrow was the best specimen from which to recover the organism.[35] In another study, 8 of 18 patients with proven histoplasmosis had a typical granuloma in the bone marrow. The organism was found in 7 patients with the silver-methenamine stain. The organisms were rare and hard to find. There was no evidence of caseating necrosis. Epithelioid cells and some giant cells were found.[36]

Epstein-Barr virus and CMV are the most frequently reported viruses to cause bone marrow granuloma. The incidence of bone marrow granuloma from EBV was about 10% in one study.[3] In a 1950 review of 23 cases of mononucleosis with bone marrow biopsies, granulomas were found in 11 of the patients (48%).[37] No characteristics were identified. Other isolated reports have associated EBV with bone marrow granuloma.[38,39] It is possible that some cases diagnosed as "mononucleosis" before the use of serologic markers are in fact due to CMV infections. With the introduction of more specific testing techniques, CMV is being recognized as a cause of bone marrow granuloma.[40]

Bone marrow granuloma is a common finding in patients with AIDS. Most of them are due to disseminated mycobacterial or fungal infections. In a study of 342 bone marrow biopsy specimens from patients with AIDS, 30% had a granuloma: 80% were related to infectious diseases, and 64% were due to mycobacterial or fungal infections. Interestingly, 20% were of undetermined cause.[31] The granulomas were subtle, small, loosely cohesive, and difficult to detect.[31] In another

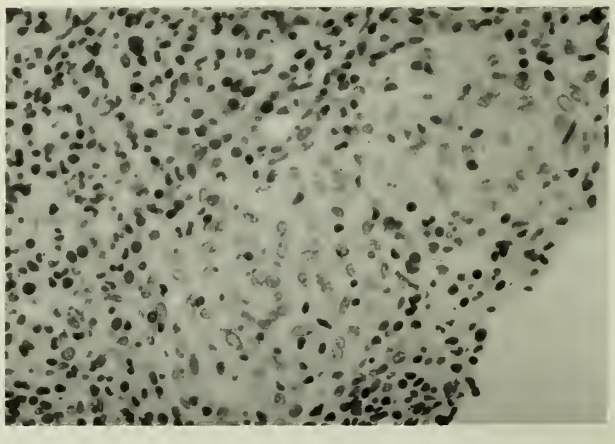

Figure 2.—An enlargement of a section of bone marrow shows giant cells (hematoxylin and eosin stain, original magnification ×40).

TABLE 2.—*Distribution of the Causes of Bone Marrow Granulomas in 5 Major Series of Bone Marrow Biopsies**

Cause	Series, No. of Cases (%)				
	Pease, 1956[3]	Badem et al, 1983[2]	White and Johnston, 1985[5]	Vilalta-Castel et al, 1988[4]	Bhargrava and Farhi, 1988[1]
Mycobacteria	19 (22)	4 (7)	24 (48)	8 (20)	10 (12)
Histoplasmosis	6 (7)	11 (19)	--	0 (0)	3 (11)
Sarcoidosis	9 (10)	4 (7)	3 (6)	2 (5)	9 (11)
Lymphoma	15 (17)	8 (14)	7 (14)	4 (10)	15 (18)
CMV or EBV	16 (18)	2 (4)	--	0 (0)	3 (3)
Malignant neoplasm	--	4 (7)	2 (4)	3 (7.5)	14 (16)
Drugs	--	7 (12)	--	--	4 (5)
Autoimmune	2 (2)	5 (9)	--	1 (2.5)	2 (2)
Unknown	--	8 (13)	--	7 (17.5)	5 (6)
Total	87	58	50	40	72

CMV = cytomegalovirus, EBV = Epstein-Barr virus

*Not all the causes of bone marrow granuloma are given; therefore, the columns do not all add up to the total in each series.

study, 35 bone marrow biopsy specimens from 34 patients with AIDS showed granulomas in the bone marrow of 4 patients (1 was due to a *Mycobacterium* species, another to a foreign body, and 2 were of undetermined origin).[41]

Foreign bodies can be present in the bone marrow. Silicosis and coal workers' pneumoconiosis have been reported in association with bone marrow granuloma. In the case of coal workers, a characteristic yellow-brown pigment was found in the granuloma.[42,43] A foreign body granuloma was also described in the bone marrow of a patient with AIDS.[41]

Isolated reports have implicated many drugs in the genesis of bone marrow granulomas. In all these cases, the granuloma was nonspecific. Usually in repeated biopsies, granulomas have been reported to disappear or at least to diminish in number after the discontinuation of the drug.[43,44] The most commonly implicated drugs are procainamide and sulfonamide.[1,2]

Sarcoidosis is one of the most frequent causes of bone marrow granuloma. It is rare for sarcoidosis to present as a granuloma in bone marrow, and isolated extrapulmonary sarcoidosis occurs in less than 5% of cases. It is responsible for 3% to 32% of the cases of bone marrow granuloma, the average being around 10%.[1-5] In one study in which 17 patients with sarcoidosis underwent bone marrow biopsy, noncaseating granulomas were found in 9 of the patients (53%).[45] Lung involvement is present in 90% to 95% of cases. The diagnosis of sarcoid depends on clinical and radiologic findings, bronchoalveolar lavage, and ACE levels. Angiotensin-converting enzyme levels have been substantially higher in patients with sarcoidosis than in those with other pulmonary diseases, but this is a nonspecific finding and should not be regarded as pathognomonic of sarcoidosis.[46-48] Most of the granulomas did not show characteristic features.[48]

Some connective tissue diseases have been associated with bone marrow granuloma. Most reports are of isolated cases.[3,4]

Finally, as many as 13% of the cases of bone marrow granuloma are of undetermined origin. In one report, a syndrome consisting of diffuse granulomatosis (affecting spleen, liver and bone marrow) with fever of unknown origin was described that responded to the administration of steroids.[49] Of 20 patients, 5 had a definitive diagnosis after long-term follow-up, but 15 remained "idiopathic." The controversy still exists whether these patients had sarcoidosis without lung involvement or a completely different disorder. Steroid therapy improved the outcome in all 15 patients.[49]

In summary, the histologic finding of a bone marrow granuloma, although rarely pathognomonic, points toward a well-known spectrum of diseases. Consideration of the clinical data and communication between the pathologist and primary care physician should help clarify the cause.

In general, strong consideration is warranted for a purified-protein derivative skin test, a sputum and bone marrow culture for AFB, a direct AFB stain, culture for fungus, and a chest x-ray film. A serologic test should be done for *H capsulatum* in areas of high prevalence, and the biopsy specimen should be carefully inspected for AFB and fungus under adequate stains. The treatment of tuberculosis should be considered until cultures are negative after six to eight weeks. Serologic testing for HIV is indicated if the diagnosis of disseminated tuberculosis, histoplasmosis, or *M avium intracellulare* is made or the patient belongs to a high-risk group.

The search for lymphoma should be thorough. Immunophenotyping of the bone marrow could be helpful. The finding of a bone marrow granuloma in patients with lymphomas must be assessed carefully because such patients are often immunocompromised and prone to the development of systemic infections with tuberculosis, histoplasmosis, CMV, and other opportunistic infections. A search for brucellosis, typhoid fever, and Q fever should depend on clinical findings. A high ACE level supports the diagnosis of sarcoidosis but is not specific.

TABLE 3.—*Differential Diagnosis of Bone Marrow Granulomas*

Malignant neoplasms	**Drugs**
Hodgkin's disease	Procainamide
Non-Hodgkin's lymphoma	Sulfonamide
Acute lymphocytic leukemia*	Chlorpropamide*
Acute myelocytic/myelogenous leukemia*	Phenylbutazone*
Chronic myelocytic/myelogenous leukemia*	Phenytoin*
Multiple myeloma*	Methyldopa*
Malignant histiocytosis*	Allopurinol*
Refractory anemia with excess blasts*	Ibuprofen*
Colon carcinoma*	Penicillamine*
Lung carcinoma*	Tolmetin sodium*
Ovarian carcinoma*	
Neuroblastoma*	**Foreign bodies**
Sarcoma*	
	Connective tissue diseases
Infectious causes	Rheumatoid arthritis*
Brucellosis	Felty's syndrome*
Typhoid fever	Primary biliary cirrhosis*
Q fever	Sjögren's disease*
Tularemia*	Pulmonary fibrosis*
Mycoplasma species*	Systemic lupus erythematosus*
Tuberculosis	Addison's disease*
Mycobacterium avium-intracellulare	Behçet's disease*
Bacillus Calmette-Guérin*	Erythema nodosum*
Leprosy*	Temporal arteritis*
Rickettsiosis*	Hemolytic anemia*
Syphilis*	Chronic renal failure
Histoplasmosis	
Cryptococcosis*	**Sarcoidosis**
Coccidioidomycosis*	
Aspergillosis*	**Idiopathic diffuse granulomatosis**
Blastomycosis*	
Epstein-Barr virus	
Cytomegalovirus	
Human immunodeficiency virus	
Hepatitis C virus*	
Herpesvirus*	

*These items are rare causes.

Drugs taken by patients should be reviewed, and those susceptible of causing a granuloma should be withdrawn if possible. The disappearance of granuloma on a later biopsy supports the diagnosis of drug-induced bone marrow granuloma.

Autoimmune diseases and other systemic diseases should be considered, depending on the clinical presentation and after the other more frequent causes of bone marrow granulomas have been ruled out. Finally, the diagnosis of idiopathic granulomatosis is a diagnosis of exclusion. Treatment with steroids has been shown to be beneficial in patients with this disorder.

REFERENCES

1. Bhargava V, Farhi DC: Bone marrow granulomas: Clinicopathologic findings in 72 cases and review of the literature. Hematol Pathol 1988; 2:43-50

2. Bodem CR, Hamory BH, Taylor HM, Kleopfer L: Granulomatous bone marrow disease—A review of the literature and clinicopathologic analysis of 58 cases. Medicine (Baltimore) 1983; 62:372-383

3. Pease G: Granulomatous lesion in the bone marrow. Blood 1956; 11: 720-734

4. Vilalta-Castel E, Valdés-Sánchez MD, Guerra-Vales JM, et al: Significance of granulomas in bone marrow: A study of 40 cases. Eur J Haematol 1988; 41:12-16

5. White RM, Johnston CL Jr: Granulomatous bone marrow disease in Virginia: Study of 50 cases. Va Med 1985; 112:316-319

6. Sacks EL, Donaldson SS, Gordon J, Dorfman RF: Epithelioid granulomas associated with Hodgkin's disease: Clinical correlations in 55 previously untreated patients. Cancer 1978; 41:562-567

7. Macavei I, Galatâr N: Bone marrow biopsy in Hodgkin's disease (HD). Morphol Embryol (Bucur) 1990; 36:25-32

8. O'Carroll DI, McKenna RW, Brunning RD: Bone marrow manifestations of Hodgkin's disease. Cancer 1976; 38:1717-1728

9. Abrams J, Pearl P, Moody M, Schimpff SC: Epithelioid granuloma revisited: Long term follow-up in Hodgkin's disease. Am J Clin Oncol 1988; 11: 456-460

10. Pak HY, Friedman NB: Pseudosarcoid granulomas in Hodgkin's disease. Hum Pathol 1981; 12:832-837

11. Tangen JM, Naess A, Aasen T, Morild I: Non-caseating granulomas in patients with hematologic malignancies. Acta Med Scand 1988; 223:83-87

12. Choe JK, Hyun BH, Salazar GH, Ashton JK, Sung CY: Epithelioid granulomas of the bone marrow in non-Hodgkin's lymphoproliferative malignancies. Am J Clin Pathol 1983; 80:19-24

13. McKenna RW, Hernandez JA: Bone marrow in malignant lymphoma. Hematol Oncol Clin North Am 1988; 2:617-635

14. Brinker H: Sarcoid reaction in malignant tumors. Cancer Treatment Rev 1986; 13:147-156

15. Montag TW, Dyer LL, Spirtos NM, James LP: Sarcoid-like lesions associated with epithelial ovarian adenocarcinoma. Obstet Gynecol 1991; 78: 978-980

16. García P, Yrivarren JI, Argumans C, Crosby E, Carrillo C, Gotuzzo E: Evaluation of the bone marrow in patients with brucellosis—Clinicopathological correlation. Enferm Infecc Microbiol Clin 1990; 8:19-24 [Eng Abstr]

17. al-Eissa YA, Assuhaimi SA, al-Fawaz IM, Higgy KE, al-Nasser MN, al-Mobaireek KF: Pancytopenia in children with brucellosis: Clinical manifestations and bone marrow findings. Acta Haematol 1993; 89:132-136

18. Gotuzzo E, Carrillo C, Guerra J, Llosa LL: An evaluation of diagnostic methods for brucellosis—The value of a bone marrow culture. J Infect Dis 1986; 153:122-125

19. Shin SM, Paik IK, Cho HI, Bone marrow pathology of culture proven typhoid fever. J Korean Med Sci 1994; 9:57-63 [Eng Abstr]

20. Akoh JA: Relative sensitivity of blood and bone marrow cultures in typhoid fever. Trop Doc 1991; 21:174-176

21. Travis LB, Travis WD, Li CY, Pierre RV: Q fever—A clinicopathologic study of five cases. Arch Pathol Lab Med 1986; 110:1017-1020

22. Srigley JR, Vellend H, Palmer N, et al: Q-fever—The liver and bone marrow pathology. Am J Surg Pathol 1985; 9:752-758

23. de Bayser L, Roblot P, Ramassamy A, Silvain C, Levillain P, Becq-Giraudon B: Hepatic fibrin-ring granulomas in giant cell arteritis. Gastroenterology 1993; 105:272-273

24. Stricker BH, Blok AP, Babany G, Benhamou JP: Fibrin ring granulomas and allopurinol. Gastroenterology 1989; 96:1199-1203

25. Young JF, Goulian M: Bone marrow fibrin ring granulomas and cytomegalovirus infection. Am J Clin Pathol 1993; 99:65-68

26. Nenert M, Mavier P, Dubuc N, Deforges L, Zafrani ES: Epstein-Barr virus infection and hepatic fibrin-ring granulomas. Hum Pathol 1988; 19:608-610

27. Ruel M, Sevestre H, Henry-Biabaud E, Courouce AM, Capron JP, Erlinger S: Fibrin ring granulomas in hepatitis A. Dig Dis Sci 1992; 37: 1915-1917

28. Moreno A, Marazuela M, Yebra M, et al: Hepatic fibrin-ring granulomas in visceral leishmaniasis. Gastroenterology 1988; 95:1123-1126

29. Vanderstigel M, Zafrani ES, Lejonc JL, Schaeffer A, Portos JL: Allopurinol hypersensitivity syndrome as a cause of hepatic fibrin-ring granulomas. Gastroenterology 1986; 90:188-190

30. Kinoshita M, Ichikawa Y, Koga H, Sumita S, Oizumi K: Re-evaluation of bone marrow aspiration in the diagnosis of miliary tuberculosis. Chest 1994; 106:690-692

31. Nichols L, Florentine B, Lewis W, Sattler F, Rarick MU, Brynes RK: Bone marrow examination for the diagnosis of mycobacterial and fungal infections in the acquired immunodeficiency syndrome. Arch Pathol Lab Med 1991; 115:1125-1132

32. Farhi DC, Mason UG 3d, Horsburgh CR Jr: The bone marrow in disseminated *Mycobacterium avium-intracellulare* infection. Am J Clin Pathol 1985; 83:463-468

33. Rosenberg SA, Seipp C, Sears HF: Clinical and immunologic studies of disseminated BCG infection. Cancer 1978; 41:1771-1780

34. Trevenen CL, Pagtakhan RD: Disseminated tuberculoid lesions in infants following BCG vaccination. Can Med Assoc J 1982; 127:502-504

35. Kauffmann CA, Israel KS, Smith JW, White AC, Schwarz J, Brooks GF: Histoplasmosis in immunosuppressed patients. Am J Med 1978; 64:923-932

36. Davies SF, McKenna RW, Sarosi GA: Trephine biopsy of the bone marrow in disseminated histoplasmosis. Am J Med 1979; 67:617-622

37. Hovde RF, Sundenberg R: Granulomatous lesions in the bone marrow in infectious mononucleosis. Blood 1950; 5:209

38. Fiala M, Colodro I, Talbert W, Ellis R, Chatterjee S: Bone marrow granulomas in mononucleosis. Postgrad Med J 1987; 63:277-279

39. Rothwell DJ: Bone marrow granuloma and infectious mononucleosis. Arch Pathol 1975; 99:508-509

40. Nosanchuk JS: Bone marrow granuloma with acute cytomegalovirus infection (Letter). Arch Pathol Lab Med 1984; 108:93-94

41. Shenoy CM, Lin JH: Bone marrow findings in acquired immunodeficiency syndrome (AIDS). Am J Med Sci 1986; 292:372-375

42. Pelstring RJ, Kim CK, Lower EE, Swerdlow SH: Marrow granulomas in coal workers' pneumoconiosis—A histopathologic study with elemental analysis. Am J Clin Pathol 1988; 89:553-556

43. Varkel Y, Braester A, Nusem D, Shkolnik T: Methyldopa-induced syndrome of inappropriate antidiuretic hormone secretion and bone marrow granulomatosis. Drug Intell Clin Pharm 1988; 22:700-701

44. Eisenstein SJ, Coleman GC: Reversible bone marrow granuloma and fever induced by phenytoin administration. J Fam Pract 1989; 29:564-565

45. Lower EE, Smith JT, Martelo OJ, Baughman RP: The anemia of sarcoidosis. Sarcoidosis 1988; 5:51-55

46. Poole GW: The diagnosis of sarcoidosis (Editorial). Br Med J 1982; 285:321-322

47. Lieberman J: Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. Am J Med 1975; 59:365-372

48. Browne PM, Sharma OP, Salkin D: Bone marrow sarcoidosis. JAMA 1978; 240:2654-2655

49. Telenti A, Hermans PE: Idiopathic granulomatosis manifesting as fever of unknown origin. Mayo Clin Proc 1989; 64:44-50

Epitomes

Important Advances in Clinical Medicine

Dermatology

Seth L. Matarasso, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association, and the summaries were prepared under the direction of Seth L. Matarasso, MD, and the panel.

Cutaneous Manifestations in Patients Infected With the Human Immunodeficiency Virus

THE SKIN IS an important end organ for diseases associated with the human immunodeficiency virus (HIV). It may be involved in important opportunistic infections. In patients with the acquired immunodeficiency syndrome (AIDS), inflammatory skin diseases such as psoriasis, eczemas, drug reactions, and pruritic folliculitis also commonly develop. These reactions are characteristic of HIV-associated skin disease and may be associated with a certain stage of the disease. Furthermore, the occurrence of skin disorders in HIV-infected patients is an important clue to the pathogenesis of common skin diseases in persons with normal immunity.

Now that most of the inflammatory skin disorders affecting HIV-infected persons have been carefully described, data have become available about their prevalence. More important, however, the skin can be used as a marker for staging HIV disease in some patients, a finding that may be useful in areas where routine helper T-cell counts are not available. Skin diseases that may occur before the development of other HIV symptoms (CD4 count $> 200 \times 10^6$ per liter) include seborrheic dermatitis, psoriasis, pruritus ani, herpes zoster, common or genital warts, oral hairy leukoplakia, oral candidiasis, and Kaposi's sarcoma. These disorders may persist throughout the course of a patient's HIV disease. Disorders seen almost exclusively once a patient has AIDS include eosinophilic folliculitis, chronic photodermatitis, persistent eczema, chronic herpes simplex, and molluscum contagiosum.

Certain skin diseases that have been presumed to have an immunologic basis occur with increased frequency in HIV-infected persons. These include seborrheic dermatitis, cutaneous drug reactions (including erythema multiforme major), psoriasis, photodermatitis, and various eczemas. Because these disorders do not occur with increased frequency in other immune-suppressed hosts, HIV somehow specifically allows their expression. This is an important clue to the pathogenesis of these skin diseases. For many years, researchers had thought that "helper" T cells were critical in the development of psoriasis. This was inconsistent with the frequent occurrence of psoriasis in patients with low helper T-cell counts. Recent studies in normal hosts with psoriasis have shown that suppressor T cells may be critical in the development of psoriatic lesions. This is more consistent with observations in HIV-infected patients. This virus, therefore, may provide an opportunity for an increased understanding of the pathogenesis of some common skin disorders.

Cryptococcosis occurs in about 6% of patients with AIDS, usually as meningitis. The prevalence of skin lesions in these patients is also 6%. Less than half of the patients with cutaneous cryptococcosis have symptoms or signs of central nervous system disease, yet all patients are positive for the serum cryptococcal antigen, and in most the cerebrospinal fluid is also positive for the cryptococcal antigen. Cutaneous cryptococcosis must be assumed to be systemic cryptococcosis, and a systemic evaluation, including lumbar puncture, is required, independent of the findings of a history and physical examination.

In patients with advanced AIDS (CD4 count $< 50 \times 10^6$ per liter), *Acanthamoeba* species may cause disease. In healthy persons and other immunocompromised hosts, these protozoa normally cause disease of the central nervous system, often encephalitis. In patients with AIDS, however, skin lesions are often the primary manifestation, and central nervous system disease occurs in only half of patients. Skin lesions are typically subcutaneous nodules that break down, forming nonhealing ulcerations covered with a serosanguinous crust. This infection is identified by skin biopsy. The organisms are abundant in tissue but difficult to identify with routine stains. Trichrome or periodic acid–Schiff stains may help. The clues to the diagnosis are skin ulcerations, chronic sinusitis (sometimes with nasal septum or hard palate perforation), and a skin

biopsy showing "vasculitis." Treatment is difficult, and the prognosis is dismal.

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REFERENCES

Berger TG: Dermatologic care in the AIDS patient in the medical management of AIDS, chap 11, *In* Sande MA, Volberding PA (Eds): The Medical Management of AIDS, 4th edition. Philadelphia, Pa, WB Saunders, 1995, pp 208-223

Muralcawa GJ, McCalmont T, Altman J, et al: Disseminated acanthamebiasis in patients with AIDS. Arch Dermatol 1995; 131:1291-1296

Pappert A, Grossman M, DeLeo V: Photosensitivity as the presenting illness in four patients with human immunodeficiency viral infection. Arch Dermatol 1994; 130: 618-623

Tumescent Technique for Local Anesthesia

THE TUMESCENT TECHNIQUE for local anesthesia has made it possible to do liposuction, dermabrasion, facelifts, carbon dioxide laser full-face resurfacing, hair transplants, and large cutaneous excisions and repairs totally by local anesthesia without intravenous sedation or narcotic analgesia. This technique is a novel approach for the delivery of local anesthesia that exploits the principle of pharmacokinetics to achieve extensive regional anesthesia of skin and subcutaneous tissue. The subcutaneous infiltration of a large volume of diluted lidocaine and epinephrine causes the targeted tissue to become swollen and firm, or tumescent, and permits a large-volume liposuction to be done entirely by local anesthesia. Depending on the clinical requirements, a tumescent anesthetic solution may contain a 5- to 20-fold dilution of the standard commercially available lidocaine (1%), epinephrine (1:100,000), and sodium bicarbonate (10 mEq per liter) in a physiologic saline solution.

A large volume of diluted epinephrine infiltrated into relatively avascular adipose tissue produces widespread prolonged and profound vasoconstriction. For a given dose, vasoconstriction diminishes the rate of systemic lidocaine absorption. This reduces both the peak plasma lidocaine concentration and the prevalence of toxicity and permits a much larger dose of lidocaine to be administered.

In fact, the tumescent technique permits safe lidocaine dosage of at least 35 mg per kg of body weight and provides effective local anesthesia for as long as ten hours. The widely accepted 7-mg-per-kg "safe maximum dose for lidocaine with epinephrine" when administered subcutaneously, as published in the *Physicians' Desk Reference* (Medical Economics, Montvale, NJ), has never been substantiated by a published scientific study.

Tumescent liposuction incorporates the tumescent technique for local anesthesia and with the use of liposuction microcannulas having an inside diameter of 2 mm and multiple small incisions for microcannular access that are not closed with sutures. Several small 2- to 3-mm incisions promote copious postoperative drainage that in turn reduces bruising, tenderness, swelling, and systemic lidocaine absorption. A description of the procedure was first published in 1987, and tumescent liposuction entirely by local anesthesia improves the safety of large-volume liposuction substantially by virtually eliminating surgical blood loss and by completely eliminating the risks of general anesthesia, intravenous sedation, or narcotic analgesia. Traditional forms of liposuction rely on general anesthesia and are associated with so much surgical blood loss that autologous blood transfusions are often routine. Many plastic and reconstructive surgical procedures thought to require general anesthesia can now be done more safely and with less discomfort when done entirely by local anesthesia. Yet, some specialists other than dermatologists are unfamiliar with tumescent anesthesia.

Certain "tumescent paradoxes" may discourage some surgeons from using the tumescent technique and could explain why the tumescent technique has yet to gain acceptance outside of dermatologic surgery:

- Diluted lidocaine at a concentration of 0.05% to 0.1% provides better and more extensive anesthesia than more concentrated commercial preparations at 1% to 2% lidocaine.
- Diluted epinephrine at concentrations of 1:2 million to 1:1 million provides better and more extensive vasoconstriction than commercial local anesthetic solutions containing epinephrine at 1:100,000.
- Smaller 2-mm cannulas permit the removal of more fat than larger 6-mm cannulas.
- Multiple small incisions without sutures leave less apparent scars than do fewer larger incisions that are closed with sutures.
- With appropriate training and skill, tumescent liposuction is less painful and more pleasant without intravenous sedation than with intravenous sedation or general anesthesia.

New therapeutic applications of tumescent drug delivery will depend on the imagination of specialists in other clinical disciplines and the nature of the clinical problems they must solve. As an example, the tumescent delivery of chemotherapeutic agents to lymphatic vessels might be applicable to the treatment and diagnosis of disease in the lymphatic system. Because some degree of local anesthesia may persist for more than 24 hours, tumescent anesthesia may prove useful for preemptive analgesia after surgical procedures such as laparotomy or saphenectomy.

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REFERENCES

de Jong RH: Local Anesthetics. St Louis, Mo, CV Mosby, 1994

Klein JA: Liposuction, *In* Moy R, Lask G (Eds): Principles and Techniques of Cutaneous Surgery. New York, NY, McGraw-Hill, 1996, pp 529-542

Klein JA: Tumescent technique chronicles local anesthesia, liposuction, and beyond. Dermatol Surg 1995; 21:449-457

Rhytides—New Approaches to Old Wrinkles

SOCIETY PUTS great emphasis on smooth, healthy skin as a sign of youth. It is no surprise, then, that many patients are seeking treatment of their facial rhytides (wrinkles).

Topical tretinoin (retinoic acid) has been recently approved by the Food and Drug Administration for the long-term correction of fine facial rhytides. Although its mechanism of action is unknown, tretinoin causes compaction of the stratum corneum and thickening of the epidermis and the dermis. This appears to be a safe and modestly effective alternative, even with long-term use.

Collagen and gelatin matrix implants are filling materials used in dermal augmentation. When a filling material is injected into the dermis, it provides a matrix around which new collagen forms; this effaces wrinkles. Bovine collagen (Zyderm) implant consists of sterile, purified, reconstituted fibrillar bovine collagen. After injection, there is only a short-lived (often only a few months) abatement of fine wrinkles because the body's own mechanisms degrade the collagen implant; this necessitates periodic maintenance injections. Cross-linked bovine collagen (Zyplast) is associated with less rapid biologic degradation but still requires periodic re-treatment. About 3% of patients have allergic reactions to bovine collagen skin tests and cannot receive this form of therapy.

Gelatin matrix implant (Fibrel) is activated by factors in a patient's own blood after intradermal administration. It is an absorbable gelatin powder that forms a matrix for complexing clotting factors with aminocaproic acid, a fibrinolytic inhibitor. Just before use, the material is mixed with the patient's plasma, which provides supplemental clotting factors. Ultimately the injected material is replaced by the patient's own collagen, and this elevates the soft tissue.

An experimental means of tissue augmentation is autologous fat transplantation. This consists of the suction-assisted removal of fat from one part of the body, followed by injecting that fat into an area of depression in another skin site. Unfortunately, transplanted fat has a short survival, except in areas like the forehead where there is bone underneath the skin.

The use of *Clostridium botulinum* A exotoxin to treat facial frown lines is currently being studied. Administering *C botulinum* toxin to the appropriate striated muscles produces reversible paralysis of the muscles that cause frown lines.

Chemical peeling (chemexfoliation) consists of the application of one or more organic acids to the skin, which produces epidermal and upper dermal sloughing. Many peeling agents are available, including α-hydroxy acids, trichloroacetic acid, and phenol. All result in varying degrees of destruction of the epidermis and portions of the dermis; the regeneration of epidermal and dermal tissues follows, with an effacement of fine facial rhytides. Phenol is the peeling agent that penetrates the deepest into the dermis. It is also quickly absorbed percutaneously. Systemic effects such as cardiac arrhythmias can occur, so full-face phenol peels require extensive preoperative evaluation and close postoperative monitoring. Trichloroacetic acid can produce superficial or deeper peels, depending on the concentration. The response to trichloroacetic acid is highly dependent on pre-peel skin preparation and the method of application. α-Hydroxy acids such as glycolic acid reduce the cohesion of the keratinocytes at low concentrations; this results in mild desquamation and epidermolysis. At higher concentrations, they produce peeling into the dermis. The duration of the positive effects is under study. Complications of chemical peeling include pigmentary changes, prolonged erythema, infections, hypertrophic scarring, changes in skin texture, and atrophy.

Dermabrasion has been used for decades for effacing shallow scars and other unwanted facial defects. It involves the use of a wire brush spun at high speeds and drawn over the surface of the skin so that the entire epidermis and upper dermis are removed. Residual portions of the skin's adnexal structures proliferate and reepithelialize the smooth-planed surface. The complications of hypertrophic scarring, pigmentary changes, loss of skin texture, and enlarged facial pores are possible problems with dermabrasion.

The resurfacing carbon dioxide laser is now being extensively used to treat mild to moderate facial rhytides. As with chemical peels and dermabrasion, carbon dioxide laser surgery uses the mechanisms of epidermal and dermal regeneration and collagen and elastin remodeling. The result is a smoothing of superficial irregularities, including fine lines and wrinkles. It has been suggested that the carbon dioxide laser optimizes its clinical results by inducing collagen and elastin shrinkage through its thermal effect. The carbon dioxide laser allows for more precise depth control and is bloodless compared with dermabrasion. A new generation of carbon dioxide lasers has led to a reduction of undesirable results such as substantial thermal injury and scarring associated with conventional continuous-wave carbon dioxide lasers. Hyperpigmentation and hypertrophic scarring are possible complications of laser resurfacing.

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REFERENCES

Fitzpatrick RE, Goldman MP: Advances in carbon dioxide laser surgery. Clin Dermatol 1995; 13:35-47

Lowe NJ, Lask G, Griffin ME: Laser skin resurfacing: Pre- and posttreatment guidelines. Dermatol Surg 1995; 21:1017-1019

Roenigk HH Jr: Treatment of the aging face. Clin Dermatol 1995; 13:245-261

Rohrich RJ, Hollier LH: Chemical peels in plastic surgery. West J Med 1995; 162:538-539

Diagnosis and Treatment of Cutaneous Herpes Simplex Virus Infections

HERPES SIMPLEX, caused by *Herpesvirus hominis* (herpes simplex virus, HSV) is one of the most common human infections. There are two major antigenic types: type 1, which is classically associated with orofacial infections, and type 2, which is usually genital. There may be substantial overlap, however. Both persist in sensory nerve ganglia after the primary infection. The virus may be reactivated and travel peripherally along efferent nerve fibers. It may be shed in saliva and genital secretions

from asymptomatic persons and may be a source of infection, although the amount shed from active lesions is from 100 to 1,000 times greater. Spread is by direct contact with infected secretions. Primary type 1 infections occur mainly in infants and young children and are often subclinical. Type 2 infections occur mainly after puberty and are usually transmitted sexually.

The virus can be inoculated into any body site. The source may be endogenous (autoinoculation), such as the transfer of infection from one body site to another, or exogenous. Following the primary infection, humoral and cell-mediated immune responses develop. They do not fully protect against primary or recurrent disease, but when immunity is deficient, such as after bone marrow transplantation or in patients with the acquired immunodeficiency syndrome, both primary and recurrent herpetic infections may be more severe and run prolonged and atypical courses.

Lesions are most commonly manifest as painful grouped vesicles on an erythematous base that rupture and become crusted. Primary infection with HSV-1 has an incubation period of four to five days and begins as a stomatitis with fever, malaise, restlessness, and excessive dribbling. Vesicles are present on the tongue, pharynx, palate, and buccal mucosa that ulcerate and become covered by a yellowish pseudomembrane. They usually heal completely in less than two weeks.

Infection with HSV-2 involves the genital areas most commonly. Painful vesicles and ulcers are most frequent on the glans, prepuce, and penile shaft in men. They last for two to three weeks if untreated. In women, similar lesions occur on the external genitalia and mucosa of the vulva, vagina, and cervix. Pain and dysuria are common. Primary herpes infection of the eye causes purulent conjunctivitis with superficial corneal ulceration. Inoculation of the fingertips results in herpetic whitlow in which there are painful deep vesicles that coalesce. Other complications that may supervene include aseptic meningitis, radiculoneuropathy, sacral paresthesia with secondary urinary retention, constipation, and in men, impotence.

After the initial infection, there may be no further clinical manifestations, or more commonly, there may be one to many recurrences. Recurrent lesions are more frequent with genital herpes than with the orolabial form. Recurrences may be triggered by minor trauma, other infections including febrile illnesses and upper respiratory tract infections, menses, ultraviolet irradiation, trigeminal neuralgia, dental surgery, or dermabrasion. In many cases, no reason for the eruption can be determined. Recurrent infections differ from primary infections by a close grouping of vesicles and the absence of constitutional symptoms. Itching or burning is the first sensation, followed by the occurrence of small, closely grouped vesicles on a red base, usually within two hours. The lesions heal in seven to ten days without scarring. Although the vesicles usually form a tightly grouped cluster, they may be arranged in a zosteriform distribution, especially in the lower thoracic or lumbar region. In such cases, there may be more severe pain, and the diagnosis may be confused with herpes zoster.

Once substantial immune suppression supervenes, lesions caused by HSV may become progressive and may be manifest by chronic ulcerative mucocutaneous lesions that persist for months. Deep crateriform ulcers of the penis, perianal area, and lip are characteristic, although ulcerative lesions on the glabrous skin may also be present. Lesions that are untreated may continue to enlarge dramatically or become verrucous and hyperplastic.

In addition to the complications discussed earlier, erythema multiforme, sometimes severe, may supervene as a consequence of previous HSV infection. Although virus cannot be seen by electron microscopy or isolated, HSV antigen has been detected around keratinocytes in the epidermis in erythema multiforme skin lesions, and HSV DNA has been demonstrated by polymerase chain reaction. This complication may develop after each episode of recurrent HSV infection and is an indication for long-term HSV suppression.

Infected epithelial cells appear swollen histopathologically, producing "ballooning degeneration." Intraepidermal vesicles are formed as a consequence of both intracellular and intercellular edema. Infected keratinocytes become dyscohesive and round up and float freely in the vesical space. The nucleoplasm of infected cells is typically pressed to the outer edge of the nuclear membrane, and intracytoplasmic and pinkish intracytoplasmic and intranuclear inclusions known as Cowdry bodies are often identifiable. Giant cells containing 2 to 15 or more nuclei are almost invariably present. The Tzanck preparation, a smear of vesicular contents stained with a Wright-Giemsa stain, is generally confirmatory because the multinucleated epithelial giant cells are readily seen. The dermis, and later the epidermis, is infiltrated with lymphocytes, neutrophils, and eosinophils.

The differential diagnosis includes other vesicular and ulcerative conditions such as irritant dermatitis; aphthous ulcers; ulcerative, opportunistic, atypical mycobacterial and deep fungal infections; and traumatic ulcers. Verrucous lesions may mimic several different conditions, including epithelial neoplasms and infections associated with pseudocarcinomatous hyperplasia. The diagnosis is made on the basis of culture, smears, biopsy, and the clinical appearance of lesions. Positive culture results usually take between one and five days and are more likely to be positive when taken from active vesicular lesions. Immunoperoxidase stains for HSV are commercially available and can increase the speed and the sensitivity of the detection of these agents. Recently a "blot" immunoprecipitation test has been developed whereby smears of vesicular fluid are placed on an antibody-impregnated paper, allowing for viral typing at the bedside.

Herpes simplex infections are treated with acyclovir at doses that range from 200 to 1,000 mg orally every four hours while awake or with famciclovir at doses of 500 mg orally every eight hours for five or more days. Valacyclovir, the hydrochloride salt of L-valine ester of acyclovir, is converted to acyclovir in the gastrointestinal tract and attains high plasma concentrations following oral administration. It has been approved for use for recurrent

HSV infections in immunocompetent hosts at a dosage of 500 mg orally twice per day. Long-term suppression with oral acyclovir is indicated in immunocompromised hosts as well as in patients who suffer recurrent erythema multiforme. Prophylactic doses are usually 400 mg twice a day. Intravenous acyclovir is rarely indicated in immunocompetent patients with HSV infection, although in some immunocompromised hosts with atrophic gastritis, the drug may not be absorbed well orally so that intravenous administration is required. Acyclovir-resistant cases in patients infected with the human immunodeficiency virus require treatment with intravenous foscarnet sodium or vidwarabine. Topical treatment with trifluorothymidine (trifluridine) and 5-(3-hydroxy-2-phosphonyl methoxy) propyl cytosine (HPMPC), an acyclic nucleoside phosphonate, has also been used effectively in some cases. Other helpful measures may include local care with cool compresses or sitz baths, topical anesthetics such as 2% to 5% lidocaine gel or ointment, and pramoxine ointment or lotion. A newly released agent, EMLA cream (a eutectic mixture of local anesthetics), may also be effective in relieving pain when applied topically under occlusion.

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REFERENCES

Coen DM: Acyclovir-resistant, pathogenic herpesviruses. Trends Microbiol 1994; 2:481-485

Corey L: Herpes simplex virus infections during the decade since the licensure of acyclovir. J Med Virol 1993; Suppl 1:7-12

Langtry JAA, Ostlere LS, Hawkins DA, Staughton RC: The difficulty in diagnosis of cutaneous herpes simplex virus infection in patients with AIDS. Clin Exp Dermatol 1994; 19:224-226

Disorders of the Female Genitalia

In the past decade, important changes have occurred in the diagnosis and management of vulvar skin disorders and chronic pain syndromes. In 1988 the International Society for the Study of Vulvovaginal Diseases replaced the old "vulvar dystrophies" nomenclature with "nonneoplastic epithelial disorders." In the new system, lichen simplex chronicus replaces "hyperplastic dystrophy" for skin thickened by rubbing or scratching. Although it is logical to call vulvar cutaneous diseases by dermatologic names, the fact that three unrelated disorders all start with the word lichen often confuses nondermatologists.

Lichen sclerosus is a progressively scarring process that gradually obliterates the vulvar architecture, narrowing the vaginal introitus. It occurs at any age and can involve other areas of the body, but does not affect vaginal mucosa. New studies have shown that clobetasol propionate 0.05% cream is far more effective in treating lichen sclerosus than 2% testosterone ointment, which is no longer recommended for any vulvar condition. The overuse of clobetasol and other high-potency corticosteroids, however, has been found to cause steroid rebound dermatitis, a rosacea-like erythema, and burning of the vulva similar to perioral dermatitis of the face.

Lichen planus is a cutaneous disease that also affects mucous membranes. A mucosal subtype of lichen planus is one of the causes of erosive or desquamative vaginitis. In other cases, a biopsy for immunofluorescence confirms bullous or cicatricial pemphigoid or pemphigus. Any erosive mucosal disorder may cause vaginal strictures and introital scarring.

Vulvodynia is defined as vulvar burning (stinging, irritation, rawness) rather than itching, which is still known as pruritus vulvae. Constant vulvodynia without visible skin signs may be a cutaneous dysesthesia (pudendal neuralgia or reflex sympathetic dystrophy). Cyclic flares of vulvovaginal irritation with or without vaginal discharge may be due to chronic recurrent candidiasis or hypersensitivity to *Candida* species. Dyspareunia may be the result of vulvar vestibulitis—introital pain at the orifices of Bartholin's and Skene's glands—or secondary vaginismus due to longstanding discomfort. Selecting the appropriate treatment depends on recognizing the primary problem. Dysesthetic vulvodynia (unremitting burning more common in postmenopausal patients) responds to low-dose tricyclic antidepressants (amitriptyline hydrochloride or nortriptyline hydrochloride) or trazodone hydrochloride, probably on the same basis that these medications are effective for postzoster neuralgia. (Younger patients with dysesthetic vulvodynia may also have interstitial cystitis, urethral syndrome, or fibromyalgia.) Cyclic vulvovaginitis gradually resolves with *Candida* species suppression with fluconazole (Diflucan, Pfizer Pharmaceuticals) or terconazole vaginal cream (Terazol Cream, Ortho Pharmaceutical) applied weekly for several months, tapering to biweekly, then monthly. Because vulvar vestibulitis that has persisted for more than a year may require local surgical excision (vestibulectomy), a gynecologic surgeon experienced in the management of vulvodynia should be consulted.

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REFERENCES

Black MM, McKay M, Braude P (Eds): Color Atlas and Text of Obstetric and Gynecologic Dermatology. London, England, Mosby-Wolfe, 1995

Pincus S, McKay M: Vulvar diseases, chap 113, *In* Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF (Eds): Dermatology in General Medicine, 4th edition. New York, NY, McGraw-Hill, 1993, pp 1463-1481

Cimetidine for the Treatment of Warts

Warts are a common dermatologic problem in children and in adults. Although various topically applied and physical treatment modalities are used to treat warts, at least 50% of them clear spontaneously within two years after their onset. In view of the discomfort and frequent physician visits associated with commonly used therapy for warts, an ideal therapy might be a parenteral medication that boosts the immune system and hastens the clearance of the wart virus.

Cimetidine has been shown to modulate the immune system, probably by blocking type 2 histamine receptors on suppressor T cells, thereby augmenting cell-mediated immunity. The administration of cimetidine increases mitogen-induced lymphocyte proliferation, inhibits suppressor T-cell function, and increases the reactivity of skin

tests. It has been used successfully to stimulate the immune system of patients with T-cell–mediated immunodeficiency disorders, such as common variable immunodeficiency and mucocutaneous candidiasis. Cimetidine also augments the clearance of atopic dermatitis and of chronic herpes zoster in immunocompromised patients and reverses the cutaneous anergy of Crohn's disease.

In an uncontrolled, open-label trial, 32 children had multiple recalcitrant common or plantar warts and were treated with cimetidine at a dosage of 25 to 40 mg per kg per day. Although improvement was not noted within the first month of therapy, at six to seven weeks, warts began to disappear. By two months, the warts had disappeared in 26 of the children (81%), with the response rate being higher in the dosing range of 30 to 40 mg per kg per day. No side effects were noted in any patient, and the warts did not tend to recur after the response to cimetidine. In an open-label prospective trial in adults, the clearance of recalcitrant warts was noted in 12 of 18 adults (67%) after three months of cimetidine therapy at a dosage of 30 to 40 mg per kg per day. Others used 1.2 grams per day of cimetidine in six patients with flat warts that had not responded to dinitrochlorobenzene immunotherapy. Four of the six cleared entirely after four weeks of treatment. A double-blind, placebo-controlled trial in children has not been done. A clearance rate of only 31% was recently noted in cimetidine-treated adults with warts, a rate not significantly different from the placebo-treated patients, but much lower than the response rate in the open-label studies in pediatric and adult patients. Further double-blind, placebo-controlled trials are needed to determine efficacy.

Although cimetidine is not approved for use in children younger than 16 years, the medication is used frequently in children with peptic ulcers and by dermatologists for urticaria, mastocytosis, and atopic dermatitis. Side effects are rare, but nausea, vomiting, diarrhea, behavioral changes, and in adolescent boys, gynecomastia have been reported. It is important to remember that cimetidine may interact with two medications commonly used in children, theophylline and phenytoin.

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REFERENCES

Gibney M, Siegfried E, Glaser D: Cimetidine for the Treatment of Refractory Verruca Vulgaris in Adults. Presented at the Society for Pediatric Dermatology meeting, 1996

Glass A, Solomon B: Cimetidine Therapy for Recalcitrant Warts in Adults. Presented at the American Academy of Dermatology meeting, 1996

New Strategies in the Management of Onychomycosis

UNTIL RECENTLY the mainstay of oral therapy for onychomycosis was griseofulvin. This compound was introduced in 1958 and was the first important oral antifungal agent available to treat dermatomycoses. After 35 years, griseofulvin is still an effective agent in the treatment of some dermatomycoses such as tinea capitis. In the treatment of pedal onychomycosis, however, typical response rates were in the order of 20% after 9 to 12 months of therapy, with relapse rates of approximately 40%. This resulted in poor compliance, and in some cases the physician or patient decided against oral therapy, given the relative ineffectiveness of available therapy.

Itraconazole, a triazole antifungal agent, has been recently approved for the treatment of dermatophyte onychomycosis in the United States. The drug is detected in the distal end of the nail plate within 7 to 14 days of starting therapy, reaching the nail plate by diffusion from both the nail bed and nail matrix. Griseofulvin is thought to enter the nail plate through the matrix region only. Following therapy with itraconazole, 200 mg per day for seven days, the drug remains in fingernails and toenails for six and nine months, respectively, after its discontinuation. Itraconazole is present at almost undetectable levels within 10 to 14 days of discontinuing treatment. With griseofulvin, the drug leaves the plasma within days of stopping therapy, and it is likely that levels in the nail plate parallel those in the plasma. Thus, griseofulvin has to be administered for a duration of 9 to 18 months while the diseased toenail is growing outward.

The favorable pharmacokinetics of itraconazole enable the drug to be administered as continuous therapy, 200 mg per day for three months, in the treatment of pedal dermatophyte onychomycosis. Pulse therapy is likely to supersede continuous therapy and is administered at three pulses of 200 mg twice a day (400 mg per day) for one week a month for three consecutive months for pedal onychomycosis. Itraconazole has a broad spectrum of activity and is effective not only against dermatophytes but also in onychomycosis due to *Candida* species and some nondermatophyte molds. The incidence of adverse effects is about 10%, with the most common being gastrointestinal disturbance, cutaneous eruption, headaches, and dizziness. The incidence of asymptomatic elevation of liver function test levels is 1% to 3%. Several drug interactions may occur with itraconazole, and a careful history of other medical conditions and concurrent medications should be obtained.

Terbinafine is an allylamine that has just been approved in the United States for the management of onychomycosis. As with itraconazole, it reaches the nail plate by both the nail matrix and the nail bed and remains in the nail plate for several months once therapy is stopped. It is effective in the treatment of dermatophyte onychomycosis, with the recommended dosage for toenail onychomycosis being continuous therapy with 250 mg per day for 12 weeks.

Limited information is available for fluconazole in the treatment of onychomycosis. This agent is more hydrophilic than itraconazole, and in published studies a dosage regimen is 150 mg once a week for about nine months.

Some topical agents that are used in Europe are amorolfine 5% lacquer, bifonazole with 40% urea paste, 8% ciclopirox nail lacquer, and 28% tioconazole. These are generally not effective when onychomycosis involves a substantial portion of the nail or when the matrix is in-

volved. In some studies, topical agents have complemented oral therapies. Chemical nail avulsion or surgical measures are more likely to be used in Europe, and in appropriate instances may be adjuncts to oral treatment.

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REFERENCES

Denning DW, Evans EGV, Kibbler CC, et al: Fungal nail disease: A guide to practice—Report of a Working Group of the British Medical Society for Medical Mycology. BMJ 1995; 311:1277-1281

Elewski BE: Onychomycosis. Fitzpatrick's J Clin Dermatol 1994; 1:48-54

Gupta AF, Sauder DN, Shear NH: Antifungal agents: An overview—Part II. J Am Acad Dermatol 1994; 30:911-933

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Alerts, Notices, and Case Reports

Retroperitoneal Hematoma as a Complication of Pudendal Block
Diagnosis Made by Computed Tomography

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INADVERTENT VASCULAR INJURY to the internal pudendal artery is the most common complication of pudendal block given for obstetric anesthesia for impending vaginal delivery. We report a case of retroperitoneal hematoma thought to arise from pudendal block. The diagnosis was made by computed tomography (CT). This is the first report on the use of such imaging to diagnose this common and probably underdiagnosed complication.

Report of a Case

The patient, a 17-year-old woman, gravida 1, para 0, was admitted for the induction of labor at 39⅔ weeks' gestation for oligohydramnios. She had an amniotic fluid index of 3.2, and intrauterine growth retardation was suspected. At 24 weeks, she was noted to have a hematocrit of 0.36 (35.7%). On admission her blood pressure was 120/68 mm of mercury, her pulse rate was 90 beats per minute, and respirations were 20 per minute. The fetus was monitored during labor with continuous electronic fetal monitoring, and the fetal heart rate showed no abnormal patterns throughout. The patient's labor progressed normally, culminating with the vaginal delivery of a female infant (2,555 grams, Apgars 8 and 9). Before delivery, a pudendal block was carried out, with the administration of 15 ml of a 1% lidocaine solution to each side. Aspiration after each injection yielded no blood return. No episiotomy was done, and a third-degree vaginal laceration resulted, which was repaired. The estimated blood loss from the delivery was 200 ml.

After the delivery, the patient had no severe abdominal pain, changes in her vital signs, or heavy vaginal bleeding. Therefore, there was no suspicion of uterine rupture, and a postpartum manual uterine exploration was not done. While in the recovery room over the next two hours, her vital signs were stable as follows: blood pressure, 124 to 141/60 to 81 mm of mercury; pulse rate, 108 to 119 beats per minute; and respirations, 18 to 20 per minute. Although she was not hypotensive, she did have a persistent tachycardia. Her vital signs also remained stable over the next three days, being in the range of the following: blood pressure, 110 to 120/70 mm of mercury; pulse rate, 80 to 100 beats per minute; and respirations, 18 to 20 per minute. Her hematocrit on admission was unknown, and therefore the magnitude of the initial drop in the hematocrit is unknown. On postpartum day 2, her hematocrit was 0.35 (35%) and dropped to 0.34 (33.7%) on postpartum day 3.

On postpartum day 2, the patient complained of abdominal distention, had decreased bowel sounds, and had a fever of 38.7°C (102°F). The next day she had back pain, pain to the right inguinal area, and persistence of fever to 38.1°C (100.6°F). Investigation for possible causes of her fever was started, and no obvious source was found, other than presumed breast engorgement; hence, the patient was discharged. Two days later, she was readmitted to the hospital with fever and chills for one day, diarrhea for three days, and increasing abdominal pain with radiation to the right lower quadrant and right flank. On examination she was noted to have a blood pressure of 132/78 mm of mercury, a pulse rate of 135 beats per minute, respirations 20 per minute, and a temperature of 38.7°C. The abdomen was mildly distended, bowel sounds were decreased, and she had voluntary guarding and pain to palpation to the right lower quadrant and right costovertebral angle. Her complete blood count showed a leukocyte count of 18.4×10^9 per liter (18,400 per mm^3), and her hematocrit was 0.29 (28.8%). Her urine showed no evidence of urinary tract infection, and there was no evidence of endomyometritis.

Because of concern over possible appendicitis versus a pelvic abscess, a CT study was done. This was performed with an intravenous contrast medium (gadolinium) using the Model 9800 General Electric CT scanner (Milwaukee, Wisconsin) and a CT-section thickness of 10 mm. Seen on CT (Figure 1) was an inhomogeneous fluid collection in the right retroperitoneal space along the iliac and psoas muscles, extending superiorly from the midpelvis to the infrarenal fossa. This fluid collection was consistent with hemorrhage. Incidentally seen was an enlarged postpartum uterus somewhat deviated to the left, which was without evidence of perforation of the uterine wall. A small amount of free fluid was present in the pelvis, and blood (lochia) was noted in the uterine cavity.

With this information, a diagnosis of an infected retroperitoneal hematoma was made, probably resulting from the perforation of a pudendal vessel in the course of the pudendal block. The patient was treated conservatively with broad-spectrum antibiotics having anaerobic coverage (ampicillin and sulbactam sodium [Unasyn;

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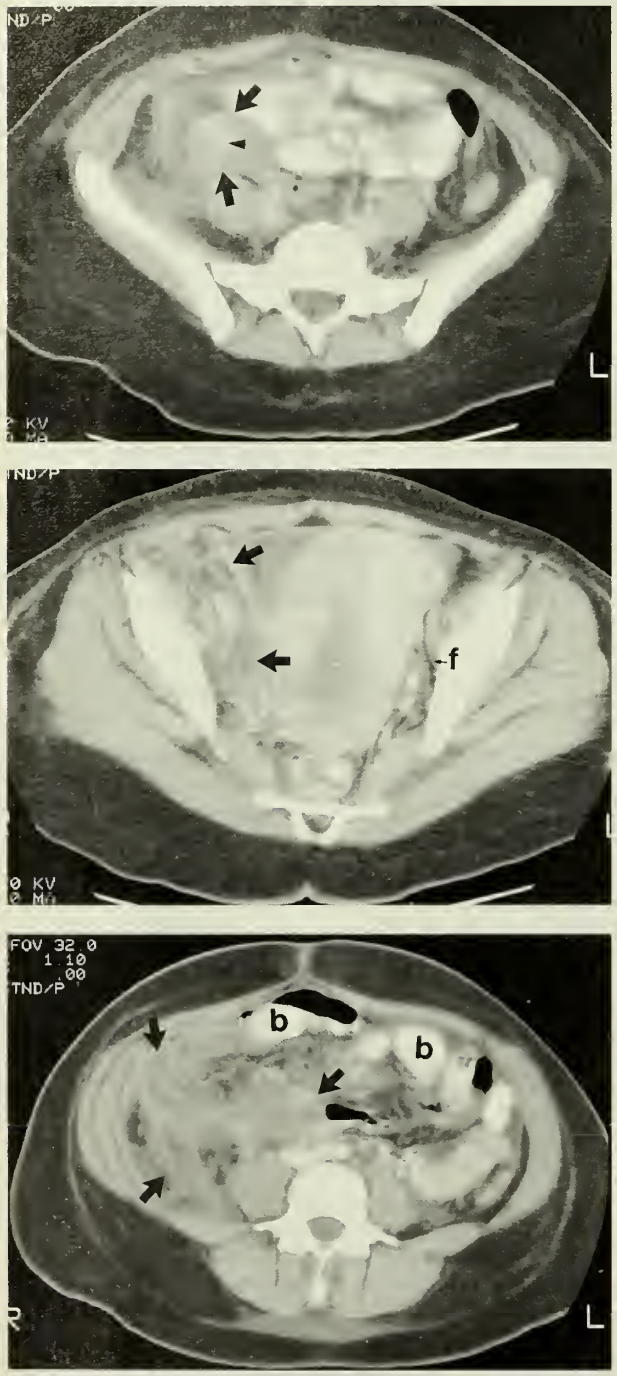

Figure 1.—Routine axial computed tomographic (CT) scan images (after the intravenous administration of contrast media) at the pelvic rim (**top**) and lower pelvis (**middle**) show abnormal heterogeneous fluid and soft tissue densities in the right retroperitoneal space along the right iliac and psoas muscles (**arrows**). The area of high density (**arrowhead**) within the lesion is consistent with hemorrhage (blood clot). The enlarged postpartum uterus is slightly deviated to the left. The normal fat planes along the right pelvic side wall are obliterated compared with the normal fat plane (**f**) on the left side. **Bottom**, An axial CT scan taken below the right renal fossa shows heterogeneous fluid and soft tissue densities (**arrows**) in the right retroperitoneal compartment along the right psoas muscle. The normal bowel loops (**b**) are displaced anteriorly and to the left.

Roerig Division]). Over the next three days, her fever and pain resolved, and her hematocrit remained stable. She was discharged on a regimen of oral antibiotics (amoxicillin and clavulanate potassium [Augmentin; SmithKline Beecham]) for an additional 14 days.

Discussion

Pudendal block is a frequently performed anesthetic procedure, accounting for 14% to 25% of all anesthetic procedures carried out in obstetrics.[1,2] An estimated 5% to 10% of patients in labor receive pudendal anesthesia. It is said to be reasonably effective and "very safe" in providing relief for lower vaginal and perineal pain.[1] The procedure is performed by the transvaginal administration of 1% lidocaine, 1% mepivacaine, or 2% chloroprocaine. A 10- or 20-ml syringe is used with a 5-in 20-gauge needle. The block is achieved by guiding the needle with the middle and index fingers through the Iowa trumpet to the tip of the ischial spine. The needle is advanced 1 cm into the sacrospinal ligament. The pudendal nerve passes just posterior to the junction of the tip of the ischial spine and the sacrospinal ligament. It is recommended to inject 3 ml of the anesthetic, advance the needle, penetrating the sacrospinal ligament, and then inject another 5 to 10 ml. An aspiration test every 2 to 3 ml is done to be assured against intravascular administration. At this point, the internal pudendal artery and vein course near the pudendal nerve. A negative aspiration test in this patient was probably a result of the needle passing cleanly through the vessel, initiating the resultant retroperitoneal bleeding. The procedure is also carried out on the contralateral side.

The pudendal nerve originates from sacral vertebrae S-2, S-3, and S-4, leaving the pelvis through the lower part of the greater sciatic foramen, curves around the ischial spine, and crosses the sacrospinal ligament posterior to it and close to its attachment to the ischial spine. It then reenters the pelvis along the internal pudendal artery at the lesser sciatic foramen. It then enters Alcock's canal, where it lies along the lateral border of the ischiorectal fossa. The pudendal nerve then breaks up into the inferior hemorrhoidal nerve, the perineal nerve, and the dorsal nerve of the clitoris. A successful pudendal block requires blocking the nerve before these terminal divisions.

The primary complications resulting from a pudendal block involve the intravascular administration of anesthetic with resultant neurotoxicity and seizures,[2] cardiotoxicity,[3] or the introduction of infection into the gluteal musculature or retropsoas space with mixed vaginal organisms.[4,5] This may be through the direct inoculation of vaginal organisms into this retropsoas space to form an abscess or seeding of these same organisms into a hematoma formed by vessel perforation (infected hematoma). It has been shown that these abscesses generally contain *Escherichia coli*, *Proteus* species, and anaerobic *Streptococcus* and *Bacteroides* species, which are vaginal flora.[4] There have been cases where these abscesses have been fatal.[5] Patients with this complication will often present after delivery with "fever of unknown origin" and pain to the hip after having received a pudendal block.[4,5] Hematomas and retropsoas or

subgluteal abscesses are recognized complications following a pudendal block,[6] but their incidence, which is low, is unknown. It has been suggested that the incidence of hematoma formation and infection of the hematoma is kept low by compression of the paravaginal tissues by the fetal head.[7(p351)]

A gallium citrate Ga 67 scan may be effective in visualizing a retropsoas abscess.[8] In this report, CT has been shown to be equally effective in visualizing such a retroperitoneal hematoma or abscess. The use of CT to diagnose retroperitoneal fluid collections was recently reviewed.[9] Retroperitoneal hemorrhage at the psoas muscle has been found by CT imaging when it arises as a consequence of a bleeding diathesis or anticoagulation, a ruptured abdominal aortic aneurysm,[9] or most frequently as a complication of femoral catheterization.[10] This is the first report of the use of CT to diagnose retroperitoneal hemorrhage complicating pudendal block. It is the diagnostic method of choice in studying retroperitoneal collections. It also is the most cost-effective technique while providing the same information about this process as can be derived from magnetic resonance imaging.

Vascular injury in the course of pudendal block is not a rare occurrence (as evidenced by positive aspiration tests). Fortunately, most patients with this injury are asymptomatic and have no sequelae, for reasons cited earlier. Physicians must, however, always remain cognizant that retroperitoneal bleeding may be life-threatening because of the possible size of this space. A key to the presence of an infected retroperitoneal hematoma is a postpartum temperature elevation in a patient with a dropping hematocrit. On the other hand, postpartum fever, usually of a wildly spiking nature that does not respond to antibiotics alone and in a patient whose hematocrit is stable, may point to a septic pelvic thrombophlebitis. The latter disorder, which is also rare—1 to 5 per 10,000 vaginal deliveries[11,12]—may similarly be diagnosed by CT imaging of the pelvis.[13-15] Septic pelvic thrombophlebitis requires the addition of heparin for a therapeutic response. Differentiating these two disorders by CT imaging could prevent a catastrophic outcome because the treatment of a patient with heparin in whom there is an underlying vessel perforation is contraindicated. Therefore, if pudendal block is followed by an unexplained fever postpartum, with hip or abdominal pain, CT may help to detect an infected retroperitoneal hematoma or abscess. Either disorder may be life-threatening or severely debilitating[4] and hence must be treated aggressively.

REFERENCES

1. Gabbe S, Niebyl JR, Simpson JL: Obstetrics—Normal and Problem Pregnancies, 2nd edition. New York, NY, Churchill-Livingstone, 1991

2. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC III: Williams Obstetrics, 19th edition. Norwalk, Conn, Appleton & Lange, 1994

3. Bozynski ME, Rubarth LB, Patel JA: Lidocaine toxicity after maternal pudendal anesthesia in a term infant with fetal distress. Am J Perinatol 1987; 4: 164-166

4. Svancarek W, Chirino O, Schaefer G Jr, Blythe JG: Retropsoas and subgluteal abscesses following paracervical and pudendal anesthesia. JAMA 1977; 237:892-894

5. Wenger DR, Gitchell RG: Severe infections following pudendal block anesthesia: Need for orthopaedic awareness. J Bone Joint Surg [Am] 1973; 55:202-207

6. Zador G, Lindmark G, Nilsson BA: Pudendal block in normal vaginal deliveries—Clinical efficacy, lidocaine concentrations in maternal and foetal blood, foetal and maternal acid-base values and influence on uterine activity. Acta Obstet Gynecol Scand (Suppl) 1974; 34:51-64

7. Bowes WA Jr: Clinical aspects of normal and abnormal labor, chap 35, *In* Creasy RK, Resnik R (Eds): Maternal Fetal Medicine—Principles and Practice, 3rd edition. Philadelphia, Pa, WB Saunders, 1994

8. Oster MW, Gelrud LG, Lotz MJ, et al: Psoas abscess localization by gallium scan in aplastic anemia. JAMA 1975; 232:377-379

9. Korobkin M, Silverman PM, Quint LE, Francis IR: CT of the extraperitoneal space: Normal anatomy and fluid collections. AJR Am J Roentgenol 1992; 159:933-941

10. Trerotola SO, Kuhlman JE, Fishman EK: Bleeding complications of femoral catheterization: CT evaluation. Radiology 1990; 174:37-40

11. Duff P, Gibbs RS: Pelvic vein thrombophlebitis: Diagnostic dilemma and therapeutic challenge. Obstet Gynecol Surv 1983; 38:365-373

12. Sweet RL, Ledger WJ: Puerperal infectious morbidity—A two year review. Am J Obstet Gynecol 1973; 117:1093-1100

13. Bahnson RR, Wendel EF, Vogelzang RL: Renal vein thrombosis following puerperal ovarian vein thrombophlebitis. Am J Obstet Gynecol 1985; 152: 290-291

14. Brown CEL, Lowe TW, Cunningham FG, Weinreb JC: Puerperal pelvic thrombophlebitis: Impact on diagnosis and treatment using x-ray computed tomography and magnetic resonance imaging. Obstet Gynecol 1986; 68:789-794

15. Angel JL, Knuppel RA: Computed tomography in diagnosis of puerperal ovarian vein thrombosis. Obstet Gynecol 1984; 63:61-64

A Human Case of Monocytic Ehrlichiosis With Adult Respiratory Distress Syndrome in Northern California

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In the United States, human monocytic ehrlichiosis is an emerging tick-borne infectious disease caused by *Ehrlichia chaffeensis*, a newly identified rickettsial agent that infects mainly mononuclear phagocytes.[1-3] Recently a human granulocytic ehrlichiosis was documented that is caused by an as-yet-unnamed *Ehrlichia* species (closely related to *Ehrlichia equi*) that infects blood granulocytes.[3-5] In both types of human ehrlichiosis, reported cases have often been in older men with a recent history of tick bite or

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
CDC = Centers for Disease Control and Prevention
Ig = immunoglobulin

exposure, and the initial illness was usually nonspecific with fever, chills, headache, malaise, myalgia, and nausea.[3,5-8] Laboratory testing often shows abnormalities such as leukopenia, thrombocytopenia, and elevated liver enzyme levels.[3,5-8]

Disease due to *E chaffeensis* was first documented in 1986,[9] and to date about 400 cases have been diagnosed from 30 states, with most cases located in the southern United States.[3,6,7] Asymptomatic *E chaffeensis* infection can occur.[10] Disease due to the newer human granulocytic *Ehrlichia* species was only recently documented, with cases from Wisconsin, Minnesota, Connecticut, and other northeastern states.[3,5,8,11] We report a probable human case of monocytic ehrlichiosis acquired in northern California.

Report of a Case

The patient, a 64-year-old man, was previously healthy without chronic medical problems. On April 1, 1994, he presented to a rural clinic in Marin County, California, because he had progressive fever, shaking chills, headache, myalgia, nausea, and malaise. On physical examination, his temperature was 39.8°C (103.6°F), and fine bibasilar rales were noted. A borderline interstitial pattern in the basilar areas was noted on a chest x-ray film. He was started on a regimen of oral cephalosporin and sent home pending blood test results.

The following day, when the patient's laboratory tests revealed a platelet count of 55×10^9 per liter (55,000 per mm^3), he was admitted to a hospital. On admission, he had a temperature of 39.2°C (102.6°F), a blood pressure of 140/90 mm of mercury, a pulse rate of 84 beats per minute, and a respiratory rate of 22 per minute, along with persistent rales in both lung bases. There was no cough, dyspnea, jaundice, rash, petechiae, or hepatosplenomegaly. He was alert and coherent but had difficulty with concentration and memory. Admission laboratory studies revealed a platelet count of 35×10^9 per liter, a leukocyte count of 5.7×10^9 per liter with a differential count of 0.55 (55%) band and 0.31 (31%) segmented forms, and a hemoglobin level of 142 grams per liter (14.2 grams per dl). A total bilirubin level was 47.9 μmol per liter (2.8 mg per dl), compared with 17.1 μmol per liter (1.0 mg per dl) the day before; the serum aspartate aminotransferase level was 87 U per liter, and the lactate dehydrogenase level was 1,171 U per liter. A prothrombin time, activated partial thromboplastin time, and fibrin-split products were within normal limits.

Despite aggressive antimicrobial therapy, his pulmonary function deteriorated progressively. He was transferred to the intensive care unit on the third hospital day and an endotracheal tube introduced on the fourth day. His clinical course and chest film findings were compatible with the adult respiratory distress syndrome (ARDS) (Figure 1). Following the placement of a Swan-Ganz catheter and appropriate fluid volume management, his pulmonary function gradually improved. He was extubated on the 22nd day and discharged home on the 26th day of his hospital stay. On discharge, mild residual infiltrates were noted on a chest film and had resolved on follow-up two months later.

TABLE 1.—*Acute, Convalescent, and Follow-up Indirect Immunofluorescence Antibody Titers for* Ehrlichia chaffeensis *in Case-Patient, Northern California, 1994*

Laboratory and Antibody Test	*Dates Serum Specimens Obtained*		
	4/4	*4/19*	*6/24*
California VRDL			
IgG	<1:8	1:32	1:128
CDC			
IgG	<1:16	≥1:512	1:256
IgM	1:32	≥1:512	<1:16

CDC = Centers for Disease Control and Prevention, Ig = immunoglobulin, VRDL = Viral and Rickettsial Disease Laboratory

Treatment with ceftizoxime sodium and clarithromycin was initially started for "broad-spectrum" coverage, including gram-negative sepsis and bacterial pneumonia. When the patient was transferred to the intensive care unit, his antimicrobial drugs were intravenous ceftizoxime, vancomycin, gentamicin sulfate, and erythromycin, the last one subsequently changed to doxycycline on the fourth hospital day for possible rickettsial agents. Within hours after the regimen of doxycycline was instituted, the patient defervesced and remained afebrile for 12 hours, the first afebrile period since admission. He had fever again the next day, however, and experienced intermittent low-grade fever for the remainder of his hospital stay despite a later addition of metronidazole and fluconazole for possible anaerobic and fungal suprainfection. He did not defervesce entirely until the endotracheal tube was removed, his total parenteral nutrition discontinued, and most of his antimicrobial agents terminated on the 22nd hospital day.

Culture of cerebrospinal fluid and repeated cultures of urine and blood were negative for pathogens, and cultures of aspirate specimens from the endotracheal tube yielded *Candida* species. Endotracheal tube and nasal aspirates were negative for *Legionella pneumophila* and influenza A and B, respectively, by direct fluorescent antibody test. Acute and convalescent sera were negative for immunoglobulin (Ig) G antibodies to *Rickettsia typhi*, *Rickettsia rickettsii*, and *Coxiella burnetii* using standardized procedures.[12] Immunoglobulin G antibodies to *E chaffeensis*, however, showed a fourfold rise (Table 1) by the immunofluorescence method using antigen provided by the Centers for Disease Control and Prevention (CDC).[1] A review of blood smears did not reveal intraleukocytic inclusion bodies.

These sera were also forwarded to the CDC where *E chaffeensis* IgG[1] and IgM (J. Dawson, CDC, Atlanta, Georgia, oral communication, January 1996) results further confirmed an incidence of recent infection (Table 1).

No hantavirus antibodies were detected. Serologic testing for *E equi* antibodies, the serologic confirmation for human granulocytic ehrlichiosis, at the University of California, Davis, was negative.

Other relevant clinical aspects of the patient's illness included hematologic, hepatic, and neurologic abnormalities. The platelet count declined to 33×10^9 per liter, and his leukocyte count reached a nadir of 2.2×10^9 per liter on the fourth hospital day. After a course of intravenous doxycycline was initiated, his platelet and leukocyte counts improved and had returned to normal by the sixth hospital day. The aspartate aminotransferase level peaked at 134 U per liter, and his total bilirubin level rose to 63.3 μmol per liter (3.7 mg per dl) before falling. Neurologically, the patient became profoundly disoriented and agitated by the third hospital day. Cerebrospinal fluid glucose and protein concentrations and cell counts were normal, as was computed tomography of his brain. He improved slowly and was fully oriented a month after discharge, but had difficulty remembering details of his hospital stay.

Of epidemiologic importance, the patient frequently hiked three to four miles in the rural coastal area near his weekend home in Marin County. He reported receiving a tick bite on the right side of his neck in mid-March, about two weeks before his illness began, and distinctly remembered the tick bleeding when it was removed and discarded. He had no pets. Five months before the onset of his illness, he traveled to New York City and Washington, DC, but did not remember any tick bite or exposure during that trip.

Discussion

To our knowledge, this is the first reported human case of ehrlichiosis acquired in California. The patient's serologic test results indicated infection with *E chaffeensis* or a closely related *Ehrlichia* species and not the recently discovered human granulocytic ehrlichiosis as antibody to *E equi* was not demonstrated. He most likely acquired the infection in northern California, probably from the reported tick bite.

His clinical presentation and illness, except for ARDS, was typical of monocytic ehrlichiosis due to *E chaffeensis* infection described previously in the southern United States.[6,7] He had nonspecific symptoms initially, and his admission laboratory tests revealed thrombocytopenia and elevated liver enzyme levels; leukopenia developed soon after he was admitted to a hospital. After a regimen of doxycycline was instituted, these abnormalities resolved. Though the patient's fever resolved initially with the use of doxycycline, its intermittent return might have been due to one or a combination of factors other than his ehrlichiosis, such as total parenteral nutrition, atelectasis, or drug allergy. The neurologic involvement was not unusual; confusion has been noted in as much as 29% of patients with ehrlichiosis, clearing slowly with appropriate treatment.[6,7]

Of clinical interest was his ARDS, which has been noted but not commonly in previous reports of ehrlichiosis. In a recent review of 237 cases of human ehrlichiosis, only 7 of the patients (3%) had pulmonary infiltrates.[7] In

Figure 1.—A chest radiograph shows diffuse bilateral infiltrates consistent with the adult respiratory distress syndrome.

an earlier review of *E chaffeensis* cases, 14 of 32 patients (44%) who had chest roentgenograms taken had evidence of pulmonary infiltrates and 4 of 38 patients (11%) had pulmonary edema; 7 required intubation and mechanical ventilation.[6] In a recent report of cases of human granulocytic ehrlichiosis, two patients who died had pulmonary infiltrates on chest films, one of whom had ARDS.[5] Pulmonary hemorrhage and secondary pneumonias due to opportunistic pathogens have been reported in fatal cases,[8,11,13,14] but were not fully evaluated in this case because the patient recovered.

Probable vectors for *E chaffeensis* in the southern United States include the ticks *Amblyomma americanum* and *Dermacentor variabilis*,[15] whereas those for the human granulocytic ehrlichiosis agent in the northeastern United States include the deer tick, *Ixodes scapularis*, which is also the tick vector for Lyme disease in that region.[16] In California, the tick vector for either agent is unknown, but *Amblyomma* species are not present. *D variabilis* ticks are in this state, however, and may be possible vectors for the monocytic ehrlichiosis that occurred in this patient.

This case report adds monocytic ehrlichiosis to the list of tick-borne infectious diseases in California. The clinical presentation is similar to that of Rocky Mountain spotted fever, another rare tick-borne infection in California. Whereas a rash is noted in as much as 90% of patients with Rocky Mountain spotted fever, it is present in less than half of those with monocytic ehrlichiosis (and rarely in patients with human granulocytic ehrlichiosis). Because doxycycline or tetracycline is the antimicrobial drug of choice for both ehrlichiosis and Rocky Mountain spotted fever, its use should be started early in suspected cases while awaiting laboratory confirmation.[3] The laboratory diagnosis for both types of *Ehrlichia* species is more commonly made serologically, although a thorough examination of initial blood smears may reveal intraleukocytic inclusions called morulae, more often with human granulocytic ehrlichiosis than with monocytic ehrlichiosis.[1,3-5,8]

Polymerase chain reaction can provide the diagnosis during acute disease, but the test is currently available in only a few research centers. In California, Rocky Mountain spotted fever and monocytic and granulocytic ehrlichioses may be confirmed by sending acute and convalescent sera to the state's Viral and Rickettsial Disease Laboratory.

Ehrlichiosis, Lyme disease, and other tick-borne infections can be prevented by taking precautions to reduce tick exposure. Clinicians should remind their patients to avoid tick-infested areas, wear protective clothing (long-sleeved shirts and long pants tucked into boots), use tick repellents, and check the body thoroughly for ticks after being in a tick-infested area.

Acknowledgment

Joseph Singleton and Theodore Tzianabos, PhD, of the Division of Viral and Rickettsial Diseases, CDC, confirmed the *Ehrlichia chaffeensis* serology; and John E. Madigan, DVM, of the School of Veterinary Medicine, University of California, Davis, confirmed the *Ehrlichia equi* serology.

REFERENCES

1. Dawson JE, Anderson BE, Fishbein DB, et al: Isolation and characterization of an *Ehrlichia* sp from a patient diagnosed with human ehrlichiosis. J Clin Microbiol 1991; 29:2741-2745

2. Anderson BE, Dawson JE, Jones DC, Wilson KH: *Ehrlichia chaffeensis*, a new species associated with human ehrlichiosis. J Clin Microbiol 1991; 29:2838-2842

3. Dumler JS, Bakken JS: Ehrlichial diseases of humans: Emerging tick-borne infections. Clin Infect Dis 1995; 20:1102-1110

4. Chen SM, Dumler S, Bakken JS, Walker DH: Identification of a granulocytotropic ehrlichia species as the etiologic agent of human disease. J Clin Microbiol 1994; 32:589-595

5. Bakken JS, Dumler JS, Chen SM, Eckman MR, Van Etta LL, Walker DH: Human granulocytic ehrlichiosis in the upper midwest United States: A new species emerging? JAMA 1994; 272:212-218

6. Eng TR, Harkness JR, Fishbein DB, et al: Epidemiologic, clinical, and laboratory findings of human ehrlichiosis in the United States, 1988. JAMA 1990; 264:2251-2258

7. Fishbein DB, Dawson JE, Robinson LE: Human ehrlichiosis in the United States, 1985-1990. Ann Intern Med 1994; 120:736-743

8. Bakken JS, Krueth J, Wilson-Nordskog C, Tilden RL, Asanovich K, Dumler JS: Clinical and laboratory characteristics of human granulocytic ehrlichiosis. JAMA 1996; 275:199-205

9. Maeda K, Markowitz N, Hawley RC, Ristic M, Cox D, McDade JE: Human infection with *Ehrlichia canis*, a leukocytic rickettsia. N Engl J Med 1987; 316:853-856

10. Yevich SJ, Sanchez JL, DeFraites RF, et al: Seroepidemiology of infections due to spotted fever group rickettsia and *Ehrlichia* in military personnel exposed in areas of the United States where such infections are endemic. J Infect Dis 1995; 171:1266-1273

11. Hardalo CJ, Quagliarello V, Dumler JS: Human granulocytic ehrlichiosis in Connecticut: Report of a fatal case. Clin Infect Dis 1995; 21:910-914

12. McDade JE, Fishbein DB: Rickettsiaceae—The rickettsiae, *In* Balows A, Hausler WJ Jr, Lennette EH (Eds): Laboratory Diagnosis of Infectious Diseases—Principles and Practices. New York, NY, Springer-Verlag, 1988, pp 864-890

13. Paddock CD, Suchard DP, Grumbach KL, et al: Brief report: Fatal seronegative ehrlichiosis in a patient with HIV infection. N Engl J Med 1993; 329:1164-1167

14. Dumler JS, Sutker WL, Walker DH: Persistent infection with *Ehrlichia chaffeensis*. Clin Infect Dis 1993; 17:903-905

15. Anderson BE, Sims KG, Olson JG, et al: *Amblyomma americanum*: A potential vector of human ehrlichiosis. Am J Trop Med Hyg 1993; 49:239-244

16. Magnarelli LA, Stafford KC III, Mather TN, Yeh M, Horn KD, Dumler JS: Hemocytic rickettsia-like organisms in ticks: Serologic reactivity with antisera to ehrlichiae and detection of DNA of agent of human granulocytic ehrlichiosis by PCR. J Clin Microbiol 1995; 33:2710-2714

Editorials

The Western Journal of Medicine—The Future Is Up to You

ABRAHAM LINCOLN said, "In times like the present, men should write nothing for which they would not willingly be responsible through time and eternity." I choose my words carefully.

On November 10, 1995, based on five years of declining membership and income and on the advice of its Executive Committee and Finance Committee, the California Medical Association (CMA) Board of Trustees voted 21 to 18 "that THE WESTERN JOURNAL OF MEDICINE (*WJM*) receive no further subsidy from the CMA, including the current $10 per member after December 31, 1995," and that "unless alternative sources of outside funding are found, the *WJM* cease printing or publication as of December 31, 1995." For the previous year, *Audio Digest*, in response to a request from the CMA to provide financial support, had signaled its interest and then likely willingness to become the journal's publisher. Before the *Audio Digest* Board's annual meeting on October 7, 1995, I was informed that they would not do this.

These actions led to a quick decision and a massive effort. The quick decision, made with *WJM*'s staff; Associate Editor Lloyd Hollingsworth Smith Jr, MD; Sandra Bressler, CMA Director of Scientific Affairs; Jack Lewin, MD, CMA Chief Executive Officer and Executive Vice President; and advisors from the CMA Board, affiliated medical societies, and others, was "Go for it: full-court press; the whole nine yards. The *Journal* must be saved." This quick decision—"*WJM*: Yes!"—led to a magnificent effort. This effort has had several parts: raising funds, maintaining the flow of new material, producing the *Journal* despite the departure of four out of six key staff members, and finding a new publisher. It is rather like filling the fuel tank and changing tires while circling the track at Indianapolis.

The effort has included the following:

- Appointing a task force that has met by conference call at least every two weeks since November 1995. Members of the task force are Sandra Bressler; Edward D. Harris Jr, MD; John Holbrook, MD; Dr Lewin; Sherman Mellinkoff, MD; Helen Ranney, MD; Joseph Silva, MD; Dr Smith; Robert D. Sparks, MD; C. John Tupper, MD; and myself. This group is strong, optimistic, and practical. Members have made creative suggestions, written dozens of letters, and made dozens of telephone calls to build support, and they have raised tens of thousands of dollars using savvy, persuasiveness, and perseverance. Their devotion to our profession and to the *Journal* is exemplary and galvanizing. They have been boon companions on a rough road.

- Publicizing the interest of the CMA in finding a publishing partner for the *WJM* while retaining ownership of it.

- Preparing a Request for Proposal; engaging a tough, highly respected consultant; and negotiating with more than 25 publishers who signed nondisclosure statements. Sandra Bressler has shouldered much of this responsibility; Anthony Edwards (*WJM*'s Editorial Manager) has prepared many of the letters and documents. Both have responded splendidly at a moment's notice. Jack Lewin has been an inspired negotiator.

- Communicating with the CMA Board and House of Delegates, western medical societies, readers, authors, and reviewers. This involves sending updates, collecting comments, and being the subject of resolutions and votes. For example, the San Francisco Medical Society submitted a resolution to the CMA House of Delegates at its annual meeting in March 1996 calling for the continued publication of the *WJM*. Reference Committee F voted to affirm CMA's commitment to THE WESTERN JOURNAL OF MEDICINE and to amend the by-laws to give the Board of Trustees latitude to negotiate with possible publishing partners. The House of Delegates approved this recommendation.

- Raising $242,000 (see page 465 for a current list of donors) to support the *Journal*'s publication through June 1996. Dr Sparks, President of the CMA Foundation, has been of incalculable value in this quest as he has applied experience, shared contacts, and practiced diplomacy. The respect and enthusiasm of the donors for the *Journal* remind me that if the situation were not so terrible, it would be wonderful.

- Enlisting CMA members in a subscription drive to test the importance of the *Journal* to its readers. The conversion from *WJM*-as-a-benefit to CMA members to *WJM*-as-a-purchase has led to more than 2,000 subscribers in four weeks at the $35-per-year rate for CMA members versus $65 per year for nonmembers. The other western medical associations have the option of retaining the *Journal* as a member benefit by allocating dues money to it. Some CMA members are angered by the possible loss of the *Journal*, an important voice of their profession, and worry that CMA has swerved away from a commitment to science and education. Others are not concerned, feeling that those activities are not central to the CMA purpose of physician advocacy. Some feel that the loss of the *Journal* is unthinkable. Others are indifferent. Some view the situation as a metaphor for the troubles of society. Others see no connection. I think the high road is in danger of being washed away by the economic rip tide.

Just what has the *Journal* done over the past century? We can look back to 1902 through the eyes of eight editors, to fruitful affiliations with 15 western medical associations and research societies and four changes of name. We have published works by thousands of authors that have been read by millions of readers, not counting press coverage. Indeed, because libraries circulate issues widely, an expert recently opined that each issue is read by

about 250,000 people. In addition to being peer-reviewed and one of the four United States members of the International Committee of Medical Journal Editors—along with the *Annals of Internal Medicine*, *Journal of the American Medical Association*, and *New England Journal of Medicine*—the *Journal* is distinguished by its devotion to publishing practical information for busy physicians—including analytical, practice-oriented health and public policy papers—recognizing that physicians have responsibilities as citizens as well as professionals. The *Journal* binds together all parts of medicine and health, primary care through subspecialties. It is part of the glue that holds our profession together.

What might the future hold? Prospects are bright, should the *Journal* make it. The Milbank Memorial Fund (a national foundation that supports health policy analysis, study, and research) has identified the *WJM* as its first choice for publishing a landmark study on the effects of managed care on patients, physicians, and other health care professionals. The papers will grow out of a conference that I will co-chair in New York City this fall. We also have plans for the *Journal* to continue publishing science-based, practical, and readable peer-reviewed papers to help keep all physicians on the cutting edge of medicine during these demanding times. We think the *Journal* should have a far wider distribution—and believe that that goal can be accomplished. We plan to continue emphasizing values and action.

So here we are, running out of time and facing eternity. History, excellence, distinction, innovations, and service are not enough when revenues fall. The *Journal*'s history shines brightly. The future depends on you, our readers. Whether you support the *Journal* because of its past and future, because of its contents, or because it is a glowing symbol of the best in medicine, your support means everything. That is why we are printing the subscription form immediately below. Your subscription is a vote to support the heart and brain, soul and spirit, so important to our profession.

LINDA HAWES CLEVER, MD
Editor

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Magnetic Resonance Imaging in Clinical Therapeutic Trials of Multiple Sclerosis

THIS ISSUE of THE WESTERN JOURNAL OF MEDICINE includes a review of magnetic resonance imaging (MRI) of multiple sclerosis lesions by Jack H. Simon, MD.[1] This article is particularly timely because currently there are more clinical therapeutic trials in multiple sclerosis recently completed, under way, or planned than ever before, essentially all of which have incorporated or will incorporate MRI. The reason for its inclusion in these trials is MRI's extraordinary sensitivity for identifying the pathology of multiple sclerosis and its safety on repeated use. For reasons that are not fully understood, however, the relevance of the MRI picture to the clinical status of individual multiple sclerosis patients has been less than optimal.

Multiple sclerosis is a difficult disease for which to establish meaningful clinical outcome measures because its natural history is one of unpredictable relapses and remissions of neurologic symptoms and signs. The patients' clinical condition usually improves spontaneously, at least temporarily, making identification of a therapeutic effect difficult. Despite the clinical fluctuations, the usual course of multiple sclerosis is one of successively less recovery from relapses and the slow development of increasingly severe residual physical disability, which is usually permanent. Previous therapeutic trials have convincingly shown that certain regimens could prophylactically decrease the severity and frequency of relapses but not alter the accumulation of physical disability over time, which is the most important factor affecting the lives of multiple sclerosis patients. The value of MRI, or any other measurement, as a clinical surrogate in multiple sclerosis must be the closeness of its match to physical disability.

As Simon points out, several studies conducted to date revealed that the correlation between the currently used MRI measures and physical disability in multiple sclerosis patients was only modest.[1] The reasons for the less-than-optimal correlation are unknown, but may relate to the fact that the most common MRI appearance of a multiple sclerosis lesion—increased signal intensities on T2-weighted images—is nonspecific and does not distinguish minimal (for example, increased water space) from severe tissue destruction (demyelination plus axonal loss). Furthermore, although gadolinium enhancement on T1-weighted images is produced by pathologically active lesions—blood-brain barrier disruption, inflammation, edema—such MRI active lesions are identified four to ten times more frequently than are clinical relapses by history and physical examination. This discrepancy may result from the fact that only a fraction of the active lesions may occur in anatomically sensitive areas of the central nervous system—optic nerves, brain stem, spinal cord—the majority occurring in areas that are relatively "silent" in terms of producing clinical symptoms and signs. Extreme examples of the MRI-clinical features mismatch include the autopsy discovery of classic multiple sclerosis lesions in the brains of patients who died of nonneurologic causes and who had been neurologically normal their entire lives.[2] Undoubtedly, most of those lesions would have been identified by MRI had it been performed during life, but these findings would have had no relevance to their clinical states. Still, there are cases in which the correlation seems particularly good. Filippi and co-workers showed that certain quantitative changes in lesions observed on serial MRIs in patients at risk because of isolated monosymptomatic syndromes could identify those in whom multiple sclerosis developed after five years.[3]

It is impossible to predict at the beginning what a given patient's course will be over the next two to five years, and, like patients with certain other relapsing diseases, those with multiple sclerosis may experience rather profound placebo effects during the course of a therapeutic trial, which must be taken into consideration. These effects have included a reduction in the clinical relapse rate by 25%[4] and changes in peripheral blood natural killer enhancement and suppression, indicating a systemic immune response.[5] Thus, whenever ethically possible, therapeutic trials in multiple sclerosis should include a randomized placebo arm to distinguish therapeutic from placebo responses. Moreover, in the recently published interferon beta-1a (Avonex, Biogen) study, which showed a substantial clinical lessening of physical disability and a benefit on the relapse rate in the interferon beta-1a–treated group, there were decreases in both T1-enhancing and T2-hyperintense lesions in the placebo-treated group as well as in those treated with the active drug (albeit not to the same extent).[6] This observation underscores the importance of a placebo-treated control group in studies assessing the efficacy of treatments on MRI-identified multiple sclerosis lesions. Whenever possible, we must be able to identify and quantitate the reduction in the lesions resulting from placebo treatment before attributing decreases observed to a given active drug therapy.

Simon clearly summarizes the natural history of multiple sclerosis lesions detected by MRI from acute through chronic stages. Obviously, an important use for MRI in future multiple sclerosis therapeutic trials will be the documentation of pathologic changes serially over time, realizing that there may be considerable discrepancy between a patient's MRI and clinical profile. Other readily identifiable uses include screening for entrance into therapeutic trials—that is, identifiable active lesions present or absent; preliminary assessment of the efficacy of a putative therapeutic agent for decreasing active lesions, which could substantially reduce the time required in phase I and II evaluations; and the use of new variables such as T1-hypointense lesion volume on standard MRI and decreases in *N*-acetyl aspartate levels on proton magnetic resonance spectroscopy, both of which may prove to be stronger surrogates of physical disability than the standard MRI measures of multiple sclerosis that are used at present.

At this time, MRI might be used as a primary outcome measure in certain small phase I and II trials for the initial assessment of therapies on active lesions. Full-fledged, pivotal phase III trials, however, must have a clinical out-

come—of which physical disability is most important—as the primary measure of efficacy, with MRI relegated to a secondary outcome status.

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REFERENCES

1. Simon JH: Magnetic resonance imaging of multiple sclerosis lesions—Basis for outcome measures in treatment trials. West J Med 1996; 164:502-509)

2. Gilbert M, Sadler M: Unsuspected multiple sclerosis. Arch Neurol 1983; 40:533-536

3. Filippi M, Horsfield MA, Morrissey SP, et al: Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology 1994; 44:635-641

4. Jacobs L, Salazar AM, Herndon R, et al: Intrathecally administered natural human fibroblast interferon reduces exacerbation of multiple sclerosis—Results of a multicenter double-blind study. Arch Neurol 1987; 44:589-595

5. Camenga DL, Johnson KP, Alter M, et al: Systemic recombinant alpha-2 interferon therapy in relapsing multiple sclerosis. Arch Neurol 1986; 43:1239-1246

6. Jacobs LD, Cookfair DL, Rudick RA, et al: Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996; 39:285-294

Hepatitis C Virus—A Pathogen for All People

HEPATITIS C VIRUS (HCV) is a positive-strand RNA virus that infects 3.5 million people in the United States and that is acquired in large part by parenteral or sexual modes of transmission.[1,2] The prevalence of HCV differs depending on the patient group under study. In patients with previous injection-drug use, the prevalence is as high as 90%; in patients with a history of posttransfusion hepatitis not due to hepatitis B, the prevalence is about 85%. Even in patients at low risk for parenterally acquired infection, healthy blood donors who have been prescreened by sophisticated questionnaires for risk factors associated with the transmission of infectious agents, the prevalence of HCV infection is about 1%. Thus, HCV is a virus that infects people in all walks of life and in all sections of society and as such represents an enormous public health problem. Three key questions must be addressed to aid clinicians in the care of these patients:

- What is the natural history of those with infection?
- Given the likely variability in natural history between patients, who are those at risk for progressive disease?
- Is effective therapy available?

The article by Tong and co-workers in the May 1996 issue of THE WESTERN JOURNAL OF MEDICINE examines the first two questions.[3] The answer to the last question is under intensive investigation, and all three questions have been incompletely resolved.

The natural history of HCV infection remains the subject of great debate. Whereas the virus persists in most of those who acquire infection, progression to clinically important liver disease occurs in some but probably the minority of those who are infected. The controversy lies in defining the proportion in whom disease develops and in determining the time over which progression to complications occurs. Discrepancies in results from different studies are likely due to differences in study design. Studies of natural history have differed in the manner in which patients have been selected (population-based studies versus referral-based studies) and the risk factor for infection (blood transfusion versus injection-drug use). In one study of patients with HCV infection and a history of previous blood transfusion who were referred to a tertiary referral center, 15% died of complications of liver disease or hepatocellular carcinoma over a four-year period.[4] Moreover, 51% of patients had cirrhosis at the initial presentation, and hepatocellular carcinoma had already developed in 5%. This study portrays HCV infection as a serious and rapidly fatal disease.

The current study of Tong and associates in the May issue of the *Journal* also included only patients referred to a liver clinic, but it examined the natural history of HCV in a somewhat younger group (mean age at presentation, 44 years) with a different risk factor for acquiring infection (injection-drug use).[4] Both of these differences are of possible relevance because the acquisition of virus by injection-drug use may carry a better short-term prognosis than the acquisition of virus by transfusion.[5,6] A person's age when the virus is acquired is also likely to be relevant because the time interval between exposure and the development of complications is probably long—20 to 30 years.[7]

Hence, if the virus is acquired early in life—for example, through a brief period of injection-drug use in the late teens or early 20s—infection would be predicted to play an important role in overall life expectancy in the ensuing decades. In contrast, if the virus is acquired later in life, comorbid conditions rather than HCV infection will likely determine life expectancy.

Tong and colleagues found in a large study group (125 patients with a history of previous injection-drug use) that at presentation, 36% had histologic evidence of cirrhosis and 0.8% had hepatocellular carcinoma. As with their study of patients with HCV infection following transfusions, the time interval between the presumed exposure (the onset of injection-drug use) and the detection of cirrhosis or hepatocellular carcinoma was long—19 and 26 years, respectively.

The rate of death was lower in the second study than in the first, however—2.4% within two years versus 15% within four years, respectively.[4] These findings support but do not prove that acquiring the virus by injection-drug use carries a better short-term prognosis than acquiring it by transfusion. The authors also attempted to examine the additive effect of alcohol use on HCV-related liver injury. One would predict that the duration of infection associated with severe disease would be shorter in those with a history of heavy alcohol use than in those without, but such an effect was not found. The confounding effect of alcohol on the natural history of HCV infection remains to be clarified.

At first glance, HCV would appear to be an aggressive pathogen in which serious liver disease occurs in the majority and progressive disease can occur over a rela-

tively short period of time. Given the manner in which patients were selected, however (assessment in a liver clinic at a specialized center), there is an inherent bias toward those with severe disease. In both studies, the proportion of patients with HCV infection in whom clinically important disease will develop could not be determined because the denominator—that is, all patients with HCV infection—was not included. This bias was avoided in a population-based study in which study patients were selected if they had an elevated serum alanine aminotransferase (ALT) level after blood transfusion and control patients were those who were transfused but in whom the serum ALT level remained normal. All-cause mortality after 18 years of follow-up was the same in both groups (about 50%), but the liver-related mortality was substantially greater in those with posttransfusion hepatitis (3.3% in the study group and 1.1% and 2.0% in the control groups). What is striking from that study is that the liver-related mortality in patients with HCV infection observed for nearly two decades is low.[8] Both this study and the first study from Tong and co-workers, however, examined the natural history of infection in patients following blood transfusion (which represents the minority of patients with HCV infection in the United States), and both studies included an older group (about 50 years of age). Thus, the extrapolation of these findings to a young group of injection-drug users may be limited.

How do we reconcile these studies? Although HCV infection causes persistent infection in almost all of those who acquire this virus, and liver disease in many, the duration of infection required to produce severe liver disease is measured in decades. Moreover, with 20 years of follow-up, life-threatening liver-related complications develop in the minority. Whether severe disease will be observed in a greater proportion with more prolonged follow-up of those infected remains to be determined. Because most injection-drug users acquire HCV infection at a young age and few have comorbid medical conditions, persistent HCV infection is a particular threat to this group. The influence of other factors such as viral genotype should also be included in any study of the natural history.[9] In the United States, injection-drug users are the largest reservoir of HCV infection, and, hence, knowledge of the natural history of infection in this group is critical to our understanding of the implications of infection with this common virus. Only when we understand the natural history of the disease, factors that influence the natural history, and those that determine disease progression will we be able to treat these patients with antiviral therapy in a cost-effective manner.

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REFERENCES

1. Alter MJ, Margolis HS, Krawczynski K, et al: The natural history of community-acquired hepatitis C in the United States—The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med 1992; 327:1899-1905

2. Terrault NA, Wright TL: Interferon for hepatitis C. N Engl J Med 1995; 332:1509-1511

3. Tong MJ, El-Farra NS: The clinical sequelae of hepatitis C acquired from injection drug use. West J Med 1996; 164:399-404

4. Tong M, El-Farra NS, Reikes AR, Co RL: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332:1463-1466

5. Mattsson L, Weiland O, Glaumann H: Chronic non-A, non-B hepatitis developed after blood transfusions, illicit self-injections or sporadically—Outcome during long-term follow-up: A comparison. Liver 1989; 9:120-127

6. Gordon SC, Elloway RS, Long JC, Dmuchowski CF: The pathology of hepatitis C as a function of mode of transmission: Blood transfusion versus intravenous drug use. Hepatology 1993; 18:1338-1343

7. Kiyosawa K, Sodeyama T, Tanaka E, et al: Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma—Analysis by detection of antibody to hepatitis C virus. Hepatology 1990; 12(pt 1):671-675

8. Seeff LB, Buskell-Bales Z, Wright EC, et al: Long-term mortality after transfusion-associated non-A, non-B hepatitis—The National Heart, Lung, and Blood Institute Study Group. N Engl J Med 1992; 327:1906-1911

9. Kobayashi M: The natural course of chronic hepatitis C—A comparison between patients with genotypes 1 and 2 hepatitis C viruses. Hepatology 1996; 23:695-699

To Lloyd Hollingsworth Smith Jr, MD: Hail and Farewell

His legion of students, residents, fellows, colleagues, tennis partners, friends, and family could tell a thousand Holly Smith stories. All are true, pointed, funny, and fit for open-minded mixed company.

"Organizations need to avoid chewing more than they bite off."

"He has mural dyslexia: he can't read the handwriting on the wall."

"Don't worry if you have to give an after-cocktails or after-dinner talk. A third of the audience is just falling asleep, a third is just waking up, and a third is engaging in private fantasies they wouldn't discuss with anyone."

One speaker who was scheduled after Holly lamented, "They say in the circus, 'Never follow the animal act.' It's worse to follow Holly Smith."

The man is far more than his bon mots, of course. Certainly, his service as Chair of the Department of Medicine at the University of California, San Francisco (UCSF), was the rocket boost that lifted the university to the top of world-class academic medical centers. He was able to accomplish that feat through his instinct for choosing strong leaders, for building, and for problem-solving. He is an achiever, not a nay-sayer; a poker-faced persuader who is his own best ace in the hole.

For the past 28 years, Holly Smith has been the Associate Editor of The Western Journal of Medicine (*WJM*). He has done this unheralded work especially on the scientific side, recruiting authors, selecting reviewers, making recommendations, and assembling each issue based on his own knowledge of the *Journal*'s inventory of papers and his flawless sense of a readable mix. He did it because it was part of his grand scheme to strengthen medicine in the West—and around the world. He considered his service to be a great privilege, but feels it is time to relinquish the responsibility. I think he prefers to pass on this baton, along with other batons, so he can sprint ahead, leading us to new heights.

Holly's departure will leave more ripples than voids. He leaves vivid memories and ripe plans. He has been a

delightful sparring partner. It must be said that he was not right every time. He could not imagine that the *Journal* might receive a foundation grant to help publish and disseminate a second special issue on cross-cultural medicine—and asserted that he would get down on his knees and kiss my ring if we did. To make it more comfortable for him when the grant came through, I stitched a pair of knee pads.

Holly, your intelligence, energy, and wisdom have placed you like Atlas, holding up the *WJM* world—and several others as well. You have strengthened us, just as you have strengthened your beloved UCSF, the Howard Hughes Medical Institute, the American Board of Internal Medicine, the Association of Professors of Medicine, the Western Society for Clinical Research, the American Society for Clinical Investigation, the Association of American Physicians, the Institute of Medicine, and on and on. Well done. Thanks. Godspeed.

LINDA HAWES CLEVER, MD
Editor

Commentary

Preserving Our Noble Heritage

JEROME P. KASSIRER, MD, *Boston, Massachusetts*

A slightly different version of this commentary was presented as the keynote speech at the 77th Annual Session of the American College of Physicians in San Francisco, California, on April 25, 1996.

Physicians have adhered to a distinguished code of professional behavior for centuries. The recent dramatic changes in our system of health care threaten this noble heritage and tempt us to abandon these principles at a time when preserving them is more important than ever.

What should we do? We should assure the public that we are professionals and that we will continue to act according to professional standards. We must assert that we are concerned first and foremost with the preservation of health and the care of the sick, and that we will continue to base our clinical judgments on a body of highly specialized scientific knowledge, not on outside forces. We must intentionally set our ideals and ethical standards high and consider them as real as earth and water. Fundamentally, these ethical standards must lead us to act in ways that are not self-serving.

The extent to which we meet these standards determines in large part how much respect the public will have for our profession, how much the public will value our services, and as a consequence, how much autonomy the public will grant us. Though we physicians have lost some of the public's respect, by and large we are still held in high regard. But the remarkable changes in the times make it more difficult to maintain the public trust. Although the ethical principles remain roughly the same as in times past, there are two new factors that make our era different. First, the temptations are stronger than ever to break the ethical rules. Second, a certain permissiveness has evolved that gives a quiet nod to relaxing these rules.

This is arguably the most tumultuous time in the history of medicine. Our successes in providing care and using technology have overtaken society's willingness to pay for them. Because of the enormous cost of care and the political ineptitude of our national leaders, the delivery of care is in a volcanic state, reforming itself day by day under market forces and erupting with new stakeholders. Instead of yesterday's familiar and comfortable model of one patient and one physician, we now have market-driven health care with vertically integrated systems, massive health maintenance organizations, huge for-profit conglomerates with hungry stockholders, and armies of health care lawyers and consultants. Each stakeholder is plucking health care dollars from the pockets of hard-working wage earners.

How is this volcano affecting medicine? In fact, its hot fingers reach everywhere. Medical education and clinical research are threatened, the survival of many public hospitals is in jeopardy, academic medical centers are making deals with the for-profit sector to bail themselves out of massive debts, and the concept of universal coverage has been abandoned.

At the same time, the amount of money that reaches physicians for the care they provide is shrinking. Less money is available from the government, employers, and insurers, and some is gobbled up by the new participants in health care. As the dollars available for patient care shrink, the temptation for physicians to maintain their incomes grows, and in this environment difficult conflicts of interest emerge. Let me consider only two, both of which threaten physicians' integrity and professionalism. The first is a familiar one—an arrangement in which physicians benefit financially from referring patients to facilities the physicians partly own such as laboratories or radiation therapy centers. A clear conflict of interest.

The second is a consequence of the change from fee-for-service medicine to a system that rewards physicians for restricting services. In this new arrangement, physicians' loyalty to patients is threatened. As managed care takes over in a community, some physicians are forced to join managed-care organizations or risk being left with few patients. When physicians join, they may be compelled to sign contracts that contain "no cause" nonrenewal clauses. Then their contracts can be terminated for any reason at all. In addition, some companies' contracts contain nondisclosure clauses that forbid physicians to tell their patients what a plan does and does not offer. Physicians under such restrictions can easily be torn between their loyalty to their patients and their loyalty to their families, because with one or two false moves they can be out of a job.

These divided loyalties that threaten physicians' livelihood are wrenching. The incentive for physicians to keep their jobs may be so strong that they may no longer be willing to act exclusively as patients' advocates. They

(Kassirer JP: Preserving our noble heritage. West J Med 1996; 164:535-536)

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may even be unwilling to advocate for a patient with management when they think that a given service is needed but is being restricted inappropriately. Physicians placed in this position simply cannot tolerate it, and that can produce an even greater threat—namely, a loss of their integrity. Soon some of them will find themselves conforming to the restrictions and deceiving themselves that what they are doing is best for the patient. In short, they will be living a lie.

These are some of the realities that threaten the preservation of medicine's noble heritage. Although the medical environment of the past three or four decades will never return, that does not mean that we won't be able to practice good medicine, and it does not mean that we won't be able to preserve our ethical heritage.

A distinguished practicing internist on the Board of Directors of the American Board of Internal Medicine makes the point that managed care is often demonized and used as a whipping boy when physicians are threatened. He says that managed care in his hands can be better than unmanaged care, because of the way it requires patients to be monitored. As an example, he mentioned that he was surprised when he applied some of the simple outcome measures of the National Center for Quality Assurance's HEDIS (Health Plan Employer Data and Information Set) criteria to his own patients and found that he fell far short of providing the kind of care he assumed he was providing. In his experience, the satisfactions and rewards can be great if a physician works within the system and truly manages the whole patient. I admit that this is only an anecdote, but it suggests that if one person can accomplish this, so can others.

How can we preserve our integrity in the new environment? First, we should admit that money isn't everything. As a venerated wise man says in Akira Kurosawa's movie, *The Seven Samurai*, "We should stop worrying about our beards when we are about to lose our heads." Second, we must be sure that our own house is in order. If a financial arrangement produces any incentive for bias, then a conflict of interest exists whether or not a physician succumbs to the temptation. These biases must be avoided if we are to preserve the trust of the public. Third, we must help develop local policies for appropriately providing services to patients. In doing so, we must base our arguments for the provision of these services on their benefits to patients. If we base our arguments instead on the need to preserve our professional autonomy or if we have some thinly veiled aim of preserving income, the public is sure to see through the façade. Fourth, we need many more people to become involved in these issues in national organizations. The ethics manual of the American College of Physicians and the professionalism report of the American Board of Internal Medicine are two examples of documents containing principles that should guide the profession through these times.[1,2] Fifth, we must continue to be agents for beneficence. We must argue for good care for those without insurance coverage, speak out against profiteering by the burgeoning medical industry, and join with national leaders in their quest for better care for the underserved and continued support for teaching and research.

We should never be discouraged about the value of medicine as a profession. After all, we are not making weapons of mass destruction, we are not selling fake jewelry on cable television, and we are not arbitraging junk bonds. Instead, we are trying our best to keep people healthy and to heal the sick. And we are making a decent living doing work that benefits people. Practicing medicine in a medical center or in the community is still a privilege to be prized.

Having expressed this optimistic vision, I want to sound a cautionary note. Our ethical standards, which have evolved over two millennia, never envisioned a market-driven health care system with incentives to undertreat patients. As members of our profession, we alone must be its keepers. We must continue to be vigilant in case the consequences of our market-driven delivery system go too far and prevent us from giving the kind of care we think appropriate. As guardians of the profession, we must decide when we have crossed the line between appropriate care and assembly-line care: when our prearranged schedule of seeing an office patient every eight minutes precludes our giving patients the personal attention they need, or when sending them home from the hospital too soon compromises their care. And what is our fallback position if we see this coming? Pellegrino summed up the answer recently in a rhetorical question[3(p1669)]:

> Should physicians accept as the standard of practice whatever legislated health care reform might require of them? Should they become enthusiastic gatekeepers on the grounds that physicians are best equipped to make microallocation decisions or because such a role allows them to maintain control of the system? . . .When is collective action by the whole profession to change the system, or to refuse outright to carry out a particular directive, morally mandatory?

Ultimately, it is individuals, not organizations, who are responsible for preserving the noble heritage of medicine. Woody Allen had it right when one of his characters in the movie *Crimes and Misdemeanors* said that we are the sum total of our choices, and Stephen Jay Gould also captures the concept in his essay, *Bully for Brontosaurus*[4(p339)]:

> There are no shortcuts to moral insight. . . .The answers to moral dilemmas are not lying out there, waiting to be discovered. They reside, like the kingdom of God, within us—the most difficult and inaccessible spot for any discovery or consensus.

It will be a test of will and resolve to be responsible, ethical, and accountable in this new environment. We must never lose sight of the fact that the way we act will be woven into who we are.

REFERENCES

1. ACP Ethics Committee: Ethics Manual [Approved by the American College of Physicians], 3rd edition. Philadelphia, Pa, American College of Physicians, 1993

2. Project Professionalism. Philadelphia, Pa, American Board of Internal Medicine, 1995

3. Pellegrino ED: Ethics. JAMA 1994; 271:1668-1670

4. Gould SJ: Bully for Brontosaurus—Reflections in Natural History. New York, NY, WW Norton, 1991

Commentary

Medical Shortage Designation

A Federal Intervention That Works

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In too many cases, the skills and knowledge of health professionals are not available to the most vulnerable groups in society. In numerous areas in the United States, basic primary health services do not exist or are extremely limited. Through the Health Resources and Services Administration's Bureau of Primary Health Care (BPHC), the federal government has sought to fill this gap by using a number of different interventions, or approaches, designed to increase access to primary health care and, ultimately, to improve the health status of underserved populations.

A lack of access to primary health care may be due to a shortage of health care professionals or the absence of an available and accessible system of care. To remedy these inadequacies, several federal, state, and local programs have been implemented to improve access to primary health services. Some of these approaches use financial incentives; others attempt to recruit professionals to underserved areas through various enticements; yet other approaches focus on the development of systems. Regardless of the adopted intervention, it is critical that program officials develop a method for targeting resources to the most needy communities in the most efficient manner.

The decision to place limited resources in a community is based on several factors. At the federal level, these factors may include legislative authority, the intent of the legislation, regulation, and guidance. Federal departments use a variety of mechanisms to direct the flow of resources to communities. In some cases, resources are allocated regionally or to states for distribution; in others, the resources are awarded directly to the community or target group. The critical component in the allocation of federal resources is the legislative authority that created the program.

The BPHC administers several programs that have specific target audiences. These activities and the method for distributing the resources are based on both the statute and the legislative intent. To illustrate this concept, we discuss two methods for distributing federal resources.

The BPHC provides grants for the support of community-based comprehensive primary care services. To be eligible to apply for this support, a community must provide information on the degree of medical underservice in the area where the services are to be provided. According to federal regulation, medical underservice is calculated by several factors in a community, such as the percentage of the population at or below the poverty level, infant mortality, the number of persons 65 years of age or older, and the ratio of primary care professionals (physicians) to the population. The capability of the requesting organization or group to provide comprehensive community-based primary care services is considered equally important. A measure of a community's need for primary care services is the foundation for a federal designation that establishes the community as a medically underserved area or as having a medically underserved population. A prudent use of public funds is a consideration before the decision to distribute resources to a community.

The other method for resource distribution is an intervention that addresses the need for primary care providers. This intervention was established by Congress to alleviate shortages of primary medical care professionals. Primary medical care professionals are defined as physicians in family practice, general internal medicine, general pediatrics, and obstetrics and gynecology; nurse practitioners; physician assistants; and certified nurse midwives. The statute clearly identifies those physicians classified as primary care. To some extent, physicians in other medical specialties may provide some form of primary care; however, their specific training is in their subspecialty. The framers of the statute thought that the specialties described in the legislation best represented primary medical care.

Specific criteria have been developed to identify communities experiencing shortages of primary medical care providers. Communities, populations, or facilities facing such shortages may apply for recruitment assistance. One type of assistance consists of incentives for primary care professionals to serve in underserved areas. Communities seeking this assistance must be designated as a health professional shortage area (HPSA). In the case of primary medical care HPSAs, the designation is based on the number of primary care physicians available to serve the area or the specific population. Other factors such as the percentages of persons at or below the poverty level, infant mortality, or low birth weight and distance or time to the

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nearest contiguous source of primary care are included in the analysis for evaluating a designation request.

Issues have been raised concerning the exclusion of nurse practitioners, physician assistants, and certified nurse midwives from the calculation of primary medical care professional ratios. The basis for this exclusion entails practice regulations that vary widely from state to state in the degree of latitude offered these providers. For example, in some states these practitioners have prescriptive authority whereas in other states they do not. Physicians maintaining an unrestricted license to practice medicine can enjoy a relatively consistent practice pattern across state lines; this is not the case for other primary care professionals. They must have the mobility to transfer nationally to fill practice gaps. In addition, the lack of uniformity in state requirements for physician assistants, nurse practitioners, and certified nurse midwives currently precludes the development of an appropriate method for enumerating these providers.

The national criteria established for the two programs were based on the legislative authority and intent as discussed in the statute. The statute did not imply any expanded use of the criteria; however, there was no prohibition placed on other federal, state, or local programs concerning the use of these criteria. As a result, federal programs have been developed that use these criteria as part of their method for allocating resources. Implementation and oversight of some of these programs, however, rest with other federal agencies.

Requests for designation are generated at the state and local levels. The responsibility for collecting data and preparing the request is borne by the applicant. In submitting a request for a designation, an applicant—usually the state health department—provides demographic data and information on the number of primary care physicians serving the area or population. The demographic data are compared with census data and other national data for the proposed service area. This information is compared with the American Medical Association's (AMA) and the American Osteopathic Association's (AOA) listings of physicians. These sources are not comprehensive listings of practicing primary care physicians; rather, they are used as guides in verifying information provided by the applicant. Discrepancies in information provided within the designation request and the AMA/AOA listings of physician are resolved between the Division of Shortage Designation and the applicant. The Division of Shortage Designation, which is in the BPHC, is charged with overseeing the designation process.

For more information on the federal shortage designation process, contact the Division of Shortage Designation at (301) 594-0816.

* * *

Commentary

Are You Being Counted?

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Are physicians being counted accurately? Physician demographic data are used in a wide variety of ways to decide what state and federal programs to pump up, leave alone, or cut back. Grants of almost unlimited variety depend on shortage designations.

In California the Office of Statewide Health Planning and Development (OSHPD), headed by David Werdegar, MD, MPH, makes recommendations to the Division of Shortage Designation, which is part of the US Department of Health and Human Services' Bureau of Primary Care. These recommendations are sometimes voted on by a commission that works closely with OSHPD.

Federally qualified health clinics and rural health clinics, both hospital-based and free-standing, depend heavily on shortage designations. These clinics are compensated using cost-based accounting. Free-standing rural health clinics have a cap of about $57 per visit. Hospital-based rural health clinics have no cap, and information contained in one hospital's disclosure report indicates that it may be getting about $136 per visit. Federally qualified health clinics have two caps, one urban and one rural. Recently the urban caps have been around $88 per visit, and the rural caps have been $76. If a county has been designated a metropolitan statistical area, however, federally qualified health clinics in communities as small as less than 5,000 people have been able to get paid at the higher cap. The payment level always seems to approach the cap when there is one.

(Feehan EB: Are you being counted? West J Med 1996; 164:538-539)

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One federally qualified health clinic with numerous locations has about 41 providers and starting physician salaries of $92,000 and is able to obtain annually grants in the neighborhood of $2 million. All this is dependent on shortage designations.

Numerous sources of data are used to determine where physicians practice. Many factors beyond a simple count of physicians enter into shortage designations. Some of these are the level of poverty, the percentage of underserved ethnic groups, high numbers in the geriatric age group, and distance to nearby sources of medical care. A facility as well as a geographic area can be designated as underserved.

The basic building blocks for counting physicians are census tracts. These are usually combined into areas called medical service study areas. The boundaries for these change from time to time, and in California, OSHPD makes recommendations, public hearings are sometimes held, and a state commission makes the final decision as to which census tracts make up particular medical service study areas.

Only primary care physicians count in deciding which areas and facilities get shortage designations. An area could theoretically have a limitless number of physician assistants, nurse practitioners, orthopedists, and general surgeons and still get designated as a shortage area. The enabling legislation for rural health clinics and federally qualified health clinics seems to have been, in part, an employment-promoting device for physician assistants and nurse practitioners. A rural health clinic or a federally qualified health clinic cannot operate without physician extenders. A physician assistant can own a free-standing rural health clinic, for example.

The State of California purchases physician demographic data. It does not purchase updates every year. The length of time between updates varies depending on who is being questioned. It would cost the state about $1 per name for it to purchase the names of the physicians being counted, and the state chooses not to buy the names. The OSHPD reports that it keeps its data up to date by checking telephone books and other sources.

Three years ago, a local hospital applied for a facility health provider shortage area designation. I asked the State of California for a copy of the raw data, and my request was declined on the grounds that the data were proprietary. The federal government, much to its credit and in pronounced contrast to the state, did send me its raw data on request.

In 1994, I wrote and published a book about the raw data—*An Analysis of Raw Data Received From the Division of Shortage Designation of the Department of Health and Human Services*. I found that there could not be more errors in the data if one tried to take good data and turn it into the most egregiously erroneous data possible. The biggest error involves confusing home addresses with practice locations. In the medical service study area known as Central Merced, the incidence of that type of error was 45.5%.This error of confusing home addresses with practice addresses is not one that tends to average out, with one such error canceling out a similar but opposite error. Physicians who care for economically distressed persons seldom live in the same census tract where their practice is. For many physicians, their entire practices were missed completely.

The types of errors were so numerous that I have proposed a new Murphy's Law: The possible errors in counting where physicians practice and what kind of practice they are in are almost limitless, with some errors occurring that are nearly unimaginable.

Another error that is frequently made is that there is no attempt to count those physicians who have internal medicine subspecialty practices but who practice substantially in the field of primary care. In addition, physicians who are teaching full-time are not supposed to be counted. This rule is being ignored completely.

Kevin Grumbach, MD, of the University of California, San Francisco, did a study in which he quoted some physician demographic figures.[1] In a conversation, he admitted that he had wondered about the accuracy of the raw data, but that he had not personally checked it. It is time for all of us to begin to check on the accuracy of physician demographic data. Most, but not all, sources of such data are inaccurate. The economic consequences of making decisions based on faulty data boggle the mind.

This is meant to be a wake-up call for the medical community. With the current volume of federally subsidized programs, it is time to insist that accurate physician demographic statistics be obtained and kept up to date. Commercially purchased data are not the place to start. States should not be using data that cannot be released to the public. States should know the names of the primary care providers they are trying to count.

REFERENCE

1. Grumbach KL, Bindman A, Seifer S, et al: Primary Care Resources and Preventable Hospitalizations in California. Berkeley, Calif, California Policy Seminars, 1995

Lessons From the Practice

All-Gummed-Up Theodorosaurus

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Little Theodore makes me want to nibble off his pink cheeks when he walks into my office. He makes me think about my own kids before my son grew a beard and my daughter traded her "blankies" and dolls for tennis rackets and cars. At 5 years old, Theodore is great at chess and prefers the Discovery Channel to Mighty Morphin' Power Rangers. His mother and father are engineers for Boeing and, as one would expect, they are attentive to details. But sometimes it is too much for them when little Theodore refuses to conduct himself within their exacting parental engineering tolerances.

His mother led him into the examination room and had him sit on the floor. She tried to explain the problem, but then became frustrated and said, "I think I better leave you two alone so he can explain this." Of course, I acquiesced, and there we were, not to play chess this time, but to address something serious weighing heavily on his mind. I wondered, what could possibly have gone wrong in this little genius's life? I looked at him, and he avoided my eyes. Then I saw a few tears. I took out my dinosaur puppets and asked him if he wanted to tell the triceratops the problem.

"That's not a triceratops, silly, that's a brontosaurus," he retorted with a devilish giggle. I was relieved. At least I had gotten him to laugh.

"So, Theodorosaurus, what's up? Why has your mum brought you in here on a nice day like this? You don't seem ill." All sorts of possibilities went through my mind as I waited, trying to tease out a response. Sometimes it is tough getting things out of kids.

He wriggled his face in embarrassment and mortification, placed his hands over his crotch, giggled, then dissolved into tears. He pulled down his pants. There was bubble gum all over his underpants and his genitals. It was a matted mess! He was humiliated by this. And I needed some time to think. There would be nothing about this in Nelson's book on pediatrics; I didn't have to open the index to know that. And the *PDR*? What's in the *PDR* about cleaning bubble gum from a child's private parts? I scrambled for humor in this situation.

Without any hesitation and with an air of great confidence and certainty, despite not having a clue about what I would do or say, I stalled for time and laughed aloud. Then I said, "Oh, Theodore. You have gum on you. How did it ever get there, I wonder? Well, that's no problem. This happens to little people all the time. I have lots of kids, just like you, who visit me every day with gum in their hair, gum on their hands, and even gum down there!" I tickled his tummy.

Wide-eyed, he looked at me in amazement. "You do? Kids have this happen all the time? How do you get it off?"

Now I was in trouble. How *do* you get gum off down there? I pulled the *PDR* from the shelf, paged through it, and mused aloud, "Hmm, weenie cleaner. . . .Oh, yes, here it is. Weenie cleaner. Yes, yes, we have some," I reassured him. I pulled petroleum jelly off the shelf. I figured that it ought to work, and it did work. I applied it and eased off what must have been the remnants of two packs of gum. As I did so, I made up the most outrageous story of how I once was called to the hospital to clean up a whole class of children who had gone to the zoo and gotten gum and cotton candy all over, and, well, it was such a mess! By then his mind was diverted, and I was able to get the gum off. He laughed and laughed! "All done. We'll have your mommy take you for something special. But enough gum for today, don't you think?"

His mother was pleased with the cure. With Theodore present, I explained to her how this was common and that there was no need for anything further in the way of admonishment. Much damage can be done to little people who become embarrassed. Sometimes they withdraw and become fearful to reveal important things. Embarrassment in children is as painful as any physical pain. On the way out, Theodore asked, "May I read some more 'bout the weenie cleaner? Can I take the *PDR* home?"

"Sorry, I need it for patients later today. But ask your parents to look it up on the Internet, Theodore. I think you'll find it there," I answered, and we all laughed. Fortunately, there's still some magic and art in what we do.

(Oppenheim EB: All-gummed-up Theodorosaurus. West J Med 1996: 164:540)

From CoMEDco, Inc, a Washington Corporation. Dr Oppenheim practiced family medicine before becoming a medical-legal consultant.
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August 15-18—**Primary Care for the Aging Person.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

August 22-25—**Implementing Change in Patient Behavior and Clinical Practice.** Picacho Hotel, Santa Fe. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

September 7-8—**New Mexico Chapter-American College of Surgeons Annual Meeting.** Inn of the Mountain Gods, Ruidoso. Sat-Sun. Contact: Catherine Musemeche, MD, UNM-Division of Pediatric Surgery, 2211 Loma Blvd NE, Albuquerque 87131.

October 3-6—**Building "Virtual" Integrated Delivery Systems: Thriving in an Advanced Healthcare Market.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 10-13—**The Managed Care Tool Box.** Pyramid Hotel, Albuquerque. Thurs-Sun. Contact: Lovelace Health Systems, National Seminar Coordinator, 5400 Gibson SE, Ed Bldg, 2nd Floor, Albuquerque 87108. (505) 262-3468. FAX (505) 262-3194.

October 25-26—**ECG Interpretation for the Primary Care Physician.** Journal Center, Albuquerque. Fri-Sat. Contact: Megan Slane, Course Coordinator, New Mexico Heart Institute, 1001 Coal Ave, SE, Albuquerque 87106. (505) 841-1000; (800) 715-6644. FAX (505) 224-7085.

February 28-March 1—**25th Annual New Mexico Thoracic Society Lung Disease Symposium.** Taos. Fri-Sat. Contact: Billie Dytzel, 216 Truman NE, Albuquerque 87108. (505) 265-0732; (800) 221-LUNG. FAX (505) 260-1739.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

July 13-20—**Update in Clinical Microbiology and Immunology.** Snow King Resort at Jackson Hole, Wyoming. Sat-Sat. 25 hrs. Contact: UUSM.

August 9-10—**Advanced Obstetrical Life Support.** University Park Hotel, Salt Lake City. 24 hrs. $450. Contact: UUSM.

August 12-16—**Northwest Neuroradiology and Advanced MR Imaging Course.** Pan Pacific Hotel, Vancouver, British Columbia. Mon-Fri. 42 hrs. $1,250. Contact: UUSM.

September 20—**Ophthalmology: Clinical Faculty Day.** Fri. 7 hrs. $65. Contact: UUSM.

October 4-5—**Western Intermountain Neurological.** University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

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(Continued from Page 549)

October 7-9—**Preconference Workshop**. Mon-Wed. $500. Limited to 15. Contact: UUSM.

October 10-13—**Intensive Interactive Head and Neck Imaging.** University Park Hotel, Salt Lake City. Thurs-Sun. 30 hrs. $750. Contact: UUSM.

December 6-12—**Intensive MR Imaging and Neuroradiology**. Marriott Hotel, Salt Lake City. Fri-Thurs. 30 hrs. $1,250. Contact: UUSM.

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ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
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MDH:	McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 625-2694.
MVH:	Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UANS:	Utah Association of Neurological Surgeons, 24 S 1100 East, Ste 302, Salt Lake City 84102. (801) 531-7806.
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VAMC:	Veterans Affairs Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 12-13—**Orthopedic Traumatology**. Seattle. Fri-Sat. Contact: U/W.

August 1-3—**Burn Update**.Seattle. Thurs-Sat. Contact: U/W.

August 5-9—**Summer Seminar in Health Care Ethics.** Seattle. Tues-Fri. Contact: U/W.

August 13-16—**Trauma Radiology**. Seattle. Tues-Fri. Contact: U/W.

August 14-17—**NW Colon and Rectal Surgeons**. Whistler. Wed-Sat. Contact: Swedish Medical Center, (206) 386-2265.

August 23. **Pain Management at the University of Washington**. Seattle. Fri. Contact: U/W.

August 23-24—**Transfusion Medicine**. Seattle. Fri-Sat. Contact: U/W.

September 5-7—**Impact of Bacterial Antibiotic Resistance on Oral Health: What is the Relevance?** Seattle. Thurs-Sat. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 6-7—**Collaborative Practice.** Seattle. Fri-Sat. Contact: U/W.

September 6-7—**Radiation Risk Communication**. Seattle. Fri-Sat. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 9-13—**24th Annual Advances in Family Practice**. Seattle. Mon-Fri. Contact: U/W.

September 18—**Random Acts in Geriatrics**. Seattle. Wed. Contact: Providence/Seattle Medical Center, (206) 320-2552.

September 19—**Diagnosis and Treatment of Peripheral Vascular Disease.** Everett. Thurs. Contact: Providence General Medical Center, (206) 261-3690.

September 20—**Cardiovascular Risk Factors**. Seattle. Fri. Contact: Virginia Mason, (206) 223-6898.

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September 24—**Washington's Children Health Policy Conference.** Seattle. Tues. Contact: Children's Continuing Medical Education, (206)526-2501.

September 25—**MHTRP—Fall Conference**. Seattle. Wed. Contact: Children's Continuing Medical Education, (206) 526-2501.

September 25-27—**Evaluation of Permanent Impairment**. Yakima and Everett. Wed-Fri. Contact: U/W Dept of Environmental Health, (206) 543-1069.

September 26-28—**Surgery Update—Harkins Society Annual Straus Lecture.** Seattle. Thurs-Sat. Contact: U/W.

September 27-28—**ACLS**. Seattle. Fri-Sat. Contact: Swedish MedicalCenter, (206) 386-2265.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

In Memoriam

California Medical Association

Anderson, Bruce, Oakland. Died Jan 24, 1996, aged 82. Graduate of Stanford University School of Medicine, Stanford, California, 1938. Licensed in California in 1938. Dr Anderson was a member of the Alameda-Contra Costa Medical Association.

❧

Borhani, Nemat O., Carnelian Bay. Died Apr 29, 1996, aged 70. Graduate of Teheran University School of Medicine, 1949. Licensed in California in 1960. Dr Borhani was a member of the Yolo County Medical Society.

❧

Borucki, David T., Monterey. Died May 7, 1996, aged 67. Graduate of Loyola University Stritch School of Medicine, Maywood, Illinois, 1954. Licensed in California in 1961. Dr Borucki was a member of the Monterey County Medical Society.

❧

Crockett, Hyrum C., Hayward. Died Mar 5, 1996, aged 92. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1930. Licensed in California in 1930. Dr Crockett was a member of the Alameda-Contra Costa Medical Association.

❧

Davis, Colbert S., Walnut Creek. Died May 15, 1996, aged 82. Graduate of Meharry Medical College, Nashville, Tennessee, 1943. Licensed in California in 1958. Dr Meharry was a member of the Alameda-Contra Costa Medical Association.

❧

Fadem, Robert S., San Diego. Died Dec 23, 1995, aged 73. Graduate of Washington University School of Medicine, St Louis, Missouri, 1947. Licensed in California in 1948. Dr Fadem was a member of the San Diego County Medical Society.

❧

Franklin, Roy W., Jr, San Bernardino. Died Apr 10, 1996, aged 54. Graduate of University of Texas Medical Branch, Galveston, 1966. Licensed in California in 1969. Dr Franklin was a member of the San Bernardino County Medical Society.

❧

Friedman, Gerald D., Richmond. Died Apr 30, 1996, aged 70. Graduate of University of Geneva, Switzerland, 1953. Licensed in California in 1955. Dr Friedman was a member of the Alameda-Contra Costa Medical Association.

Fujimoto, Ronald K., Martinez. Died Apr 17, 1996, aged 59. Graduate of Northwestern University Medical School, Chicago, Illinois, 1963. Licensed in California in 1966. Dr Fujimoto was a member of the Alameda-Contra Costa Medical Association.

❧

Hanfling, Stanley M., San Mateo. Died May 11, 1996, aged 65. Graduate of Cornell University Medical College, New York, New York, 1955. Licensed in California in 1960. Dr Hanfling was a member of the San Mateo County Medical Association.

❧

Hardegen, Gary L., Anaheim. Died Dec 8, 1995, aged 48. Graduate of University of Maryland School of Medicine, Baltimore, 1974. Licensed in California in 1979. Dr Hardegen was a member of the Orange County Medical Association.

❧

Hulme, Russell L., Los Gatos. Died Feb 20, 1996, aged 70. Graduate of University of Utah School of Medicine, Salt Lake City, 1952. Licensed in California in 1954. Dr Hulme was a member of the Santa Clara County Medical Association.

❧

Humphreys, C. Fillmore, Berkeley. Died Apr 23, 1996, aged 72. Graduate of Washington University School of Medicine, St Louis, Missouri, 1953. Licensed in California in 1953. Dr Humphreys was a member of the Alameda-Contra Costa Medical Association.

❧

Miano, Benedict D. A., San Bernardino. Died Feb 25, 1996, aged 88. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1935. Licensed in California in 1936. Dr Miano was a member of the San Bernardino County Medical Society.

❧

O'Brien, Thomas Francis, Blythe. Died Feb 15, 1996, aged 68. Graduate of Georgetown University School of Medicine, Washington, DC, 1956. Licensed in California in 1958. Dr O'Brien was a member of the Riverside County Medical Association.

❧

Pallais, Armando R., Oxnard. Died Dec 10, 1995, aged 79. Graduate of University of Southern California School of Medicine, 1943. Licensed in California in 1943. Dr Pallais was a member of the Ventura County Medical Society.

Queary, Charles H., Jr, St Helena. Died Apr 13, 1996, aged 75. Graduate of University of Colorado School of Medicine, Denver, 1944. Licensed in California in 1949. Dr Queary was a member of the Napa County Medical Society.

❧

Saran, Richard, Napa. Died Feb 25, 1996, aged 73. Graduate of University of Michigan School of Medicine, Ann Arbor, 1954. Licensed in California in 1973. Dr Saran was a member of the Napa County Medical Society.

❧

Smart, Bret, Oakland. Died Jan 11, 1996, aged 86. Graduate of University of California, San Francisco, School of Medicine, 1935. Licensed in California in 1935. Dr Smart was a member of the Alameda-Contra Costa Medical Association.

❧

Smith, Sam W., Lemon Grove. Died May 2, 1996, aged 63. Graduate of University of Kansas School of Medicine, Lawrence, 1959. Licensed in California in 1970. Dr Smith was a member of the San Diego County Medical Society.

❧

Tessa, Clement D., North Hollywood. Died Jan 14, 1996, aged 72. Graduate of University of California, Irvine, 1962. Licensed in California in 1975. Dr Tessa was a member of the Forty-First Medical Society.

Denver Medical Society

Rest, Arthur C., Denver. Died Mar 22, 1996, aged 92. Graduate of University of Illinois, Chicago, 1928. Licensed in Colorado in 1937. Dr Rest was a member of the Denver Medical Society.

New Mexico Medical Society

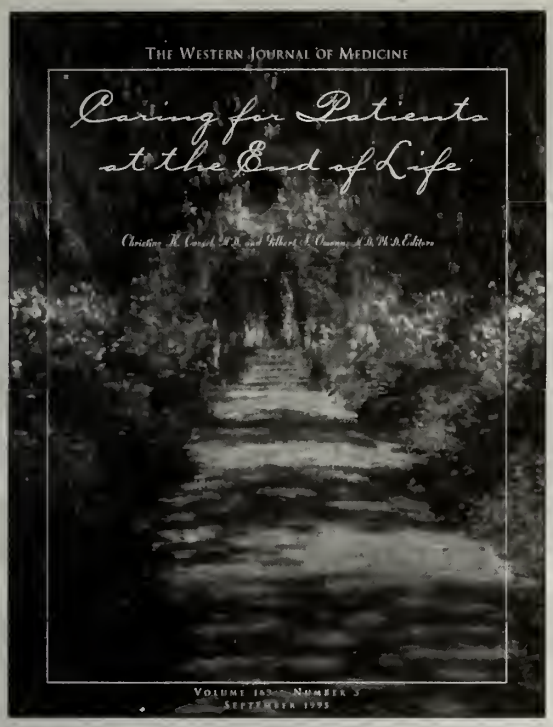
Bronitsky, Jacob, Albuquerque. Died Apr 12, 1996, aged 88. Graduate of University of Vienna, 1935. Licensed in New Mexico in 1966. Dr Bronitsky was a member of the Greater Albuquerque Medical Association.

❧

McIntire, Robert W., Carlsbad. Died Apr 1996, aged 78. Graduate of University of Kansas School of Medicine, Kansas City, 1943. Licensed in New Mexico in 1946. Dr McIntire was a member of the Eddy County Medical Society.

Wyoming Medical Society

Volk, Joseph R., Died Feb 12, 1996, aged 75. Graduate of University of Nebraska College of Medicine, Omaha, 1952. Licensed in Wyoming in 1952. Dr Volk was a member of the Goshen County Medical Society.



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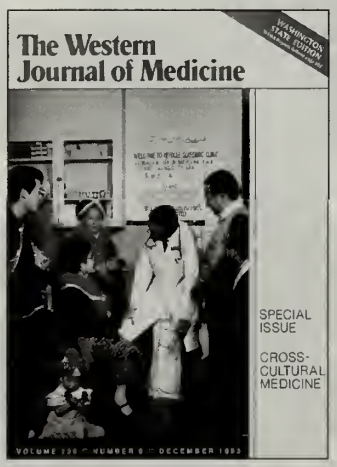

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Colorado Medical Society–PO Box 17550, Denver 80217-0550. (303) 779-5455. September 20-22, 1996, Steam Boat Sheraton, Steam Boat Springs.

Hawaii Medical Association–1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 18-20, 1996, Kauai Marriott, Lihue.

Idaho Medical Association–305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 23-26, 1997, Sun Valley Inn, Sun Valley.

Montana Medical Association–2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: August 16-18, 1996, West Yellowstone Conference Hotel, West Yellowstone.

Nevada State Medical Association–3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 1-4, 1997, Sheraton El Conquistador Hotel, Tuscon, AZ.

New Mexico Medical Society–7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: TBA.

Utah Medical Association–540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 25-28, 1996. University Park Hotel, Salt Lake City.

Washington State Medical Association–900 United Airlines Bldg, 2033 6th Ave, Ste 1100, Seattle 98121. (206) 441-9762. Annual Meeting: September 26-28, 1996. Tacoma Sheraton, Tacoma.

Wyoming Medical Society–PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 11-14, 1997, Jackson Lake Lodge, Moran.

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Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

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2:35 AM Prints tracer letters to all insurance carriers who are late in paying. Sends appeal letters to those carriers who have underpaid. Produces letters to patients identifying those services denied. Makes notations of correspondence in patient records.

2:48 AM Produces personal letters to recall patients for return appointments. Notes the follow-up on each patient's record.

3:15 AM Checks the appointment calendar for the day and prints an accurate schedule for each provider. Prepares a superbill for each patient due in for the day.

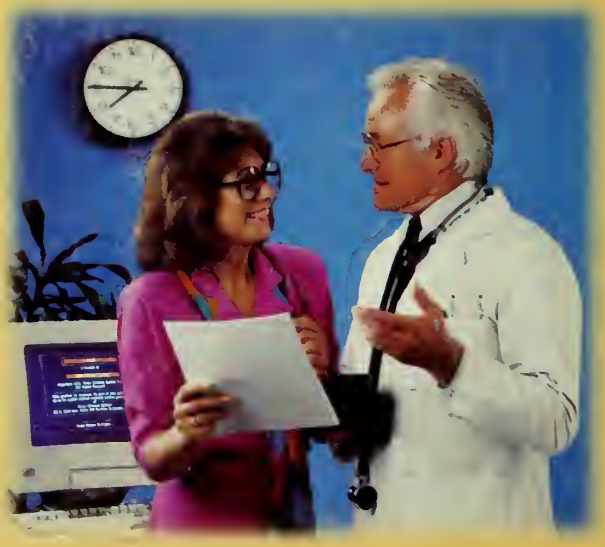
3:50 AM Automatically dials and transmits yesterday's claims to Medicare and Medi-Cal. Prints receipt acknowledgments and makes notations of the claim process in each patient's record.

4:22 AM Reviews all patients' ledgers and builds a report, listing each collection job for the next day.

5:10 AM Performs critical full system backup on tape drive.

7:35 AM Turns on coffee maker.

7:45 AM **On-Staff 2000** awaits your arrival with all completed paperwork and a *hot pot of coffee*!!!



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